



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 29

A. R. Katritzky &  
A. J. Boulton

Advances in  
**Heterocyclic  
Chemistry**

Volume 29

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Advances in

# HETEROCYCLIC CHEMISTRY

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## Preface

Volume 29 consists of six contributions. Three of these deal with specific groups of compounds and update previous contributions in this publication on the same type of compounds. Thus, R. K. Smalley, who writes on "The Chemistry of Indoxazenes and Anthranils: 1966–1979," updates the article by Wünsch and Boulton published in 1967 in Volume 8. Raymond Bonnett and Stephanie A. North, writing on "The Chemistry of the Isoindoles," update the contribution by White and Mann, published in Volume 10, in 1969, and Richard M. Scrowston, with his review entitled, "Recent Advances in the Chemistry of Benzo[*b*]-thiophenes," updates that by himself and Iddon in Volume II, published in 1970. The chemistry of "Furoxans and Benzofuroxans" is covered by A. Gasco and A. J. Boulton. This and the subject of "Mononuclear Heterocyclic Rearrangements" reviewed by Michele Ruccia, Nicolò Vivona, and Domenico Spinelli, are both topics close to the hearts of the Editors of this volume. Finally, Yasumitsu Tamura and Masazumi Ikeda have summarized "Advances in the Chemistry of Heteroaromatic *N*-Imines and *N*-Aminoazonium Salts." Although this subject was reviewed as recently as 1974, in Volume 17 of *Advances*, its growth since then has been so dramatic that this further review is very timely.

A. R. KATRITZKY  
A. J. BOULTON

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# The Chemistry of Indoxazenes and Anthranils: 1966–1979

R. K. SMALLEY

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University of Salford, Salford, England*

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## I. Introduction

This review is an update of the article published in 1967.<sup>1</sup> As in the original review, and for the same reasons, the ring systems are referred to mainly by their common names, indoxazene and anthranil, rather than as 1,2- and 2,1-benzisoxazoles. No attempt has been made to be fully comprehensive, particularly with the large number of patent references. Emphasis has been placed on discussing new aspects of benzisoxazole chemistry and significant adaptations, variations, and improvements to traditional preparative methods.

Noteworthy advances include the use of 7-hydroxyindoxazanium salts as peptide coupling agents, the ease of decarboxylation of indoxazene-3-carboxylic acids in dipolar aprotic solvents (Section II,C,2,a), and the photorearrangement and -decomposition of indoxazenes to benzoxazoles and *o*-hydroxyacylbenzenes, respectively (Section II,C,2,c). In addition, the thermal rearrangement of 3-arylanthranils to acridones (Section III,C,5,a), the elucidation of the structures of the so-called anthranil *N*-oxides (Section III,E), and the photodecomposition of anthranils (Section III,C,7) are also of special interest.

The sections follow the same general order as in the original review although some major changes will be apparent. In addition to *Chemical Abstracts*, many of the major primary journals have been scanned to the end of 1979.

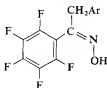
<sup>1</sup> K.-H. Wünsch and A. J. Boulton, *Adv. Heterocycl. Chem.* **8**, 277 (1967).

## II. Indoxazenes (1,2-Benzisoxazoles)

### A. PREPARATION

#### 1. From *o*-Halogenobenzoyl Compounds

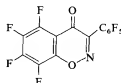
Base-promoted ring closure of *o*-halogenobenzophenone oximes remains a useful preparative route to 3-aryl- and 3-heteroarylindoxazenes.<sup>2-6</sup> Of particular note are the cyclizations of the polyfluorobenzyl ketoximes (**1**; Ar = Ph or C<sub>6</sub>F<sub>5</sub>) in hot dimethylformamide to the tetrafluoro- and perfluorindoxazenes (**2**; R = CH<sub>2</sub>Ph and CH<sub>2</sub>C<sub>6</sub>F<sub>5</sub>, respectively).<sup>7</sup> In dimethylformamide at 100°C the monoxime of perfluorobenzyl cyclizes to 3-(perfluorobenzoyl)indoxazene (**2**; R = COC<sub>6</sub>F<sub>5</sub>) (61%) accompanied by a minor amount (2%) of the perfluorobenzoxazinone **3**.<sup>7</sup>



(1)



(2)



(3)

#### 2. From *o*-Nitrophenylacetic Acid and Its Derivatives

Oximes of type **4**, prepared by nitrosation of 2,6- and 2,4-dinitrophenylacetic acid derivatives, cyclize in strong base, e.g., sodium hydride in 1,2-dimethoxyethane, to indoxazene-3-carboxylic acid derivatives, e.g., **5** (R = OMe or NHAr).<sup>8-10</sup>

<sup>2</sup> R. Jacquier, C. Petrus, F. Petrus, and M. Valentin, *Bull. Soc. Chim. Fr.*, 2672 (1970).

<sup>3</sup> R. R. Tidwell, J. D. Geratz, O. Dann, G. Volz, D. Zeh, and H. Loewe, *J. Med. Chem.* **21**, 613 (1978).

<sup>4</sup> G. Pagliavini, G. Cignarella, and E. Testa, *Farmaco, Ed. Sci.*, **20**, 686 (1965).

<sup>5</sup> V. J. Bauer, W. J. Fanshawe, and G. E. Wiegand, U.S. Patent 3,678,062 (1972) [CA **77**, 114403 (1972)].

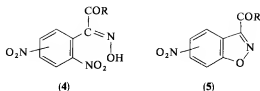
<sup>6</sup> J. Laforest and G. Thuillier, *J. Heterocycl. Chem.* **14**, 793 (1977).

<sup>7</sup> G. S. Shchegoleva, M. I. Kollegova, and V. A. Barkhash, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 126 (1971) [CA **77**, 101494 (1972)]; G. S. Shchegoleva and V. A. Barkhash, *ibid.*, 123 (1971) [CA **77**, 48316 (1972)].

<sup>8</sup> D. S. Kemp and K. G. Paul, *J. Am. Chem. Soc.* **97**, 7305 (1975); D. S. Kemp, D. D. Cox, and K. G. Paul, *ibid.*, 7312.

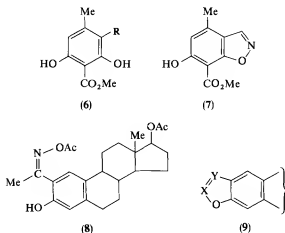
<sup>9</sup> T. S. Straub and M. L. Bender, *J. Am. Chem. Soc.*, **94**, 8875 (1972).

<sup>10</sup> S. K. Shah, M. R. Patel, and B. N. Mankad, *Indian J. Chem.* **9**, 1311 (1971).



### 3. From *o*-Hydroxybenzoyl Oximes and Related Compounds

The thermal decomposition of *o*-hydroxybenzoyl *O*-acyloximes constitutes a valuable synthetic route to indoxazenes. Traditionally, the decompositions are carried out under reduced pressure or in boiling acetic anhydride.<sup>1</sup> Recently, however, sodium carbonate in boiling triglyme,<sup>11</sup> and boiling dry pyridine<sup>12</sup> have been used to effect cyclization of a wide range of *o*-hydroxyaldoxime and -ketoxime acetates, generally in near quantitative yields. Occasionally side reactions compete with indoxazene formation. For example, the *O*-acetate **6** (*R* = CH=NOAc) at 180°C yields only the nitrile (**6**; *R* = CN). However, in boiling xylene the indoxazene **7** is formed in 80% yield.<sup>13</sup> The estradiol oxime **8** on treatment with *p*-toluene- or benzenesulfonyl chloride in pyridine undergoes Beckmann rearrangement, then cyclization to the benzoxazole (**9**; X = CMe. Y = N), whereas with benze-



<sup>11</sup> J. C. Saunders and W. R. N. Williamson, *J. Med. Chem.* **22**, 1554 (1979); British Patent, 1,488,044 (1977) [CA 88, 120799 (1978)]; Ger. Offen. 2,450,053 (1973) [CA 83, 97263 (1975)].

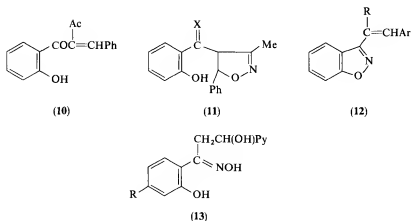
<sup>12</sup> K. A. Thakar, D. D. Goswami, and B. M. Bhawal, *Indian J. Chem.* **15B**, 1058 (1977); K. A. Thakar and B. M. Bhawal, *ibid.*, 1061.

<sup>13</sup> D. H. R. Barton, B. Halpern, Q. N. Porter, and D. J. Collins, *J. Chem. Soc. C*, 2166 (1971).

sulfonyl chloride in dilute potassium hydroxide the indoxazene (**9**; X = N, Y = CMe) becomes the sole product.<sup>14</sup>

Cyclization conditions also seem to be of paramount importance in determining the products from the ring closure of *o*-hydroxy- $\alpha$ -acylchalcone (**10**).<sup>15</sup> Treatment of **10** with hydroxylamine hydrochloride in pyridine furnishes the oxime (**11**; X = NOH) of the *o*-hydroxybenzoylisoxazoline (**11**; X = O), the product from the action of hydroxylamine hydrochloride and sodium acetate on the chalcone. In contrast, with ethanolic hydroxylamine hydrochloride, **10** yields only the indoxazene (**12**; R = Ac, Ar = Ph).

Ketoximes (**13**; R = H or OMe; Py = 2-, 3-, or 4-pyridyl) in hot polyphosphoric acid cyclize to 3-ethenylindoxazenes (**12**; R = H, Ar = pyridyl) rather than to the expected pyridylchromanones.<sup>16</sup>



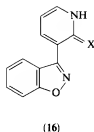
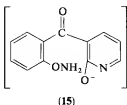
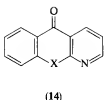
In contrast to 2- and 4-azaxanthone, 1-azaxanthone (**14**; X = O) does not yield an oxime under normal conditions. However, with hydroxylamine hydrochloride in an excess of hot ethanolic potassium hydroxide it ring-opens to give a mixture of the indoxazene **16** (X = O) and the oxime of 3-salicyloyl-2-pyridone.<sup>17</sup> Under strongly basic conditions (sodium hydride in dimethylformamide) the indoxazene (**16**) is the only product, a result which leads the authors to conclude that **16** arises not from the pyridone but by direct attack of  $\text{NH}_2\text{O}^-$  on the azaxanthone followed by ring closure of the resulting intermediate (**15**). 3-Azaxanthone and 1-azathioxanthone (**14**; X = S) behave similarly, the latter furnishing the pyridothione (**16**; X = S) in 77% yield.

<sup>14</sup> P. Crabbé, L. A. Maldonado, and I. Sanchez, *Tetrahedron* **27**, 711 (1971).

<sup>15</sup> Z. Jerzmanowska and W. Basinski, *Rocz. Chem.* **47**, 1785 (1973).

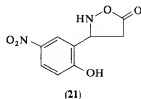
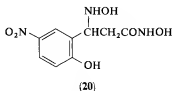
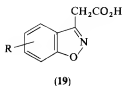
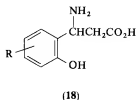
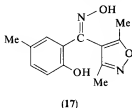
<sup>16</sup> K. Samulá, *Rocz. Chem.* **48**, 959 (1974).

<sup>17</sup> F. J. Villani, J. Hannon, E.-A. Wefer, and T. A. Mann, *J. Org. Chem.* **40**, 1734 (1975).



An unusual base-induced transformation is apparent during the cyclization of 2,6-dihydroxyacetophenone oxime.<sup>18</sup> In aqueous methanol with potassium hydroxide (0.5 equivalents) a quantitative yield of 4-hydroxy-3-methylindoxene is produced. However, as the ratio of hydroxide ion to oxime is increased, the isomeric 4-hydroxy-2-methylbenzoxazole begins to form, reaching a maximum yield (80%) at a hydroxide ion to oxime ratio of 12:1. 2-Hydroxy-4-methoxy- and 2,4-dihydroxyacetophenone oximes do not undergo this unprecedented and as yet unexplained ring closure. Dehydration of the salicyloylisoxazole oxime (17) in concentrated sulfuric acid produces a mixture of 3-(3,5-dimethyl-4-isoxazolyl)-5-methylindoxazene and the corresponding isomeric benzoxazole and not, as was first assumed, a mixture of benzopyranooxadiazines.<sup>19</sup>

The structures of the by-products from the action of hydroxylamine on 6- and 7-methylcoumarin have now been confirmed as 5- and 6-methylindoxazene-3-acetic acid, respectively.<sup>1,20</sup> Careful investigation shows that with a large excess of hydroxylamine coumarins form 1:3 adducts which



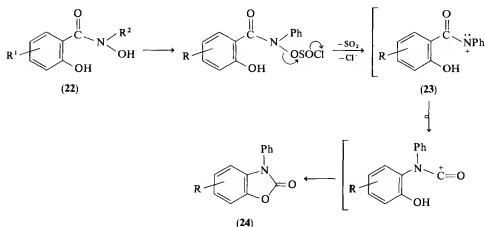
<sup>18</sup> P. Crabbé, A. Villarino, and J. M. Muchowski, *J. C. S. Perkin I*, 2220 (1973).

<sup>19</sup> F. Eiden and W. Löwe, *Tetrahedron* **28**, 3295 (1972).

<sup>20</sup> G. Casini, F. Gualtieri, and M. L. Stein, *J. Heterocycl. Chem.* **6**, 279 (1969).

disproportionate in boiling ethanol to a mixture of amino acids (**18**) (75–80%), *o*-hydroxyacetophenone oximes (5–10%), and indoxazene-3-acetic acids (**19**) (10–20%).<sup>21</sup> A smaller excess of hydroxylamine not only increases the yield of **19**, but also, in some instances (e.g.,  $R = NO_2$ ), permits isolation of a 1:2 adduct (**20**) (see also Section II,D,1). The isoxazolinone **21**, formed by cyclization of **20** in dilute acetic acid, rearranges in boiling ethanol to **19** ( $R = 5-NO_2$ ). The method has been adapted for the synthesis of a number of indoxazene-3-acetic acids and their methyl and ethyl esters, which are of interest as isosteres of indole-3-acetic acids.<sup>21,22</sup>

The reaction of thionyl chloride with salicylhydroxamic acids (**22**;  $R^2 = H$ ) has been developed as a general synthetic method for 3-hydroxy-indoxazenes.<sup>1,23</sup> An improvement of this two-stage process is claimed by treating the hydroxamic acids with carbonyl diimidazole in boiling tetrahydrofuran followed by acidification.<sup>24</sup>



SCHEME 1

A report that *N*-phenylsalicylhydroxamic acids (**22**;  $R^2 = Ph$ ) on treatment with thionyl chloride yield *N*-phenyl-1,2-benzisoxazolinones is incorrect. The products are in fact *N*-phenylbenzoxazolinones (**24**), which arise by a Lössen-type rearrangement of the acylnitrenium intermediate (**23**) as outlined in Scheme 1.<sup>25</sup>

<sup>21</sup> M. Giannella, F. Gualtieri, and M. L. Stein, *J. Heterocycl. Chem.* **8**, 397 (1971).

<sup>22</sup> M. Giannella, F. Gualtieri, and C. Melchiorre, *Phytochemistry* **10**, 539 (1971).

<sup>23</sup> H. Böshagen, *Chem. Ber.* **100**, 954 (1967).

<sup>24</sup> R. Friary and B. R. Sunday, *J. Heterocycl. Chem.* **16**, 1277 (1979).

<sup>25</sup> T. Sheradsky and S. Avramovici-Grisaru, *Tetrahedron Lett.*, 2325 (1978).

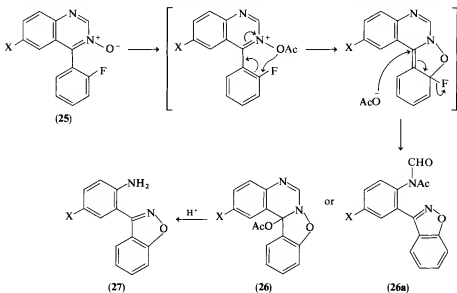
The action of cold thionyl chloride on salicylhydroxamic acids, and on *o*-hydroxyaldoximes and -ketoximes, is a versatile synthetic route to 3-hydroxy-, 3-unsubstituted, and 3-alkylindoxazenes.<sup>26</sup>

#### 4. Miscellaneous Methods

Cycloadditions involving nitrile oxides are normally associated with the production of reduced indoxazenes (see Section II,D). However, with benzyne as the dipolarophile, 3-substituted indoxazenes may be prepared.<sup>27</sup>

The *O*-acetate of 3-methyl-5-nitrobenzophenone oxime on thermolysis at 165°C under reduced pressure (20 mm) yields 5-methyl-7-nitro-3-phenylindoxazene (78%).<sup>28</sup> The 5-methyl-6-nitro isomer is prepared similarly.

4-(2-Fluorophenyl)quinazoline 3-oxides (**25**; X = Cl or H) on treatment with acetic anhydride undergo an unusual intramolecular nucleophilic displacement of fluorine to yield the benzisoxazolo[2,3-*c*]quinazolines **26**, which on acid hydrolysis ring-open to 3-(*o*-aminophenyl)indoxazenes (**27**) (Scheme 2).<sup>29</sup> (The alternative structure **26a** seems likely for the intermediate.)



SCHEME 2

<sup>26</sup> U. R. Kalkote and D. D. Goswami, *Aust. J. Chem.* **30**, 1847 (1977).

<sup>27</sup> T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **42**, 826 (1969).

<sup>28</sup> B. Arventiev and H. Offenbergl, *An. Stiint Univ. "Al. I. Cuza" Iasi, Sect. 1c* **13**, 61 (1967) [*CA* **69**, 26938 (1968)].

<sup>29</sup> A. Walser, T. Flynn, and R. I. Fryer, *J. Heterocycl. Chem.* **11**, 885 (1974).

The indoxazenes are also obtained directly from the *N*-oxides by vigorous alkaline hydrolysis.

### B. PHYSICAL AND SPECTROSCOPIC PROPERTIES

The electronic spectrum, ionization potential and electron affinity,  $\pi$ -electron distribution, and total  $\pi$  energy of indoxazene have been calculated by semiempirical Pariser-Parr-Pople SCF and modified CNDO-CI methods.<sup>30-32</sup> Generally, the results are in good agreement with experimentally determined values. Calculated ground-state  $\pi$ -electron densities indicate that C-5 and C-7 are the most nucleophilic sites and predict for the carbocyclic ring electrophilic and nucleophilic substitution orders of  $7 > 5$  and  $3 > 4 = 6$ .<sup>30</sup> The former prediction is not borne out by experiment as most electrophilic substitutions take place at the 5-position (see Section II,C,1). Also calculated are the orbital energies of the highest occupied ( $-\epsilon_{\text{HO}}$  9.31) and lowest vacant ( $-\epsilon_{\text{LV}}$  1.44) molecular orbitals and the total  $\pi$  energy of the system ( $E_{\pi}$  -337.17).

The He(I) photoelectron, <sup>14</sup>N-NMR, and high-resolution <sup>1</sup>H-NMR spectra of indoxazene have been measured and are reproduced in references 33, 34, and 35, respectively.

A study has been made of the chemical shifts of the methyl group in a comprehensive series of quaternized azoles and their benzologs, *N*-methyl-indoxazanium perchlorate being one of the compounds reported.<sup>36</sup>

Analysis of metastable ion abundancies and shape has demonstrated that indoxazene isomerizes into *o*-cyanophenol prior to fragmentation in the mass spectrometer.<sup>37</sup>

Calculations, by variable integral methods, of  $\pi$ - $\pi^*$  transitions for indoxazenes are in good agreement with experimental data.<sup>38</sup> Ultraviolet spectra of 3-hydroxyindoxazenes and of several indoxazene-3-carboxylic acids are available.<sup>8,23</sup> On the basis of ultraviolet studies it is concluded that indoxazenes are weaker bases than the corresponding isoxazoles.<sup>39</sup> Similar

<sup>30</sup> M. Kamiya, *Bull. Chem. Soc. Jpn.* **43**, 3344 (1970).

<sup>31</sup> Y. Ferré, R. Faure, and E.-J. Vincent, *J. Chim. Phys. Physicochim. Biol.* **69**, 860 (1972).

<sup>32</sup> S. D. Carson and H. M. Rosenberg, *J. Mol. Spectrosc.* **32**, 242 (1969).

<sup>33</sup> M. H. Palmer and S. M. F. Kennedy, *J. Mol. Struct.* **43**, 203 (1978).

<sup>34</sup> L. Stefaniak, *Bull. Acad. Pol. Sci., Ser. Sci. Chem.* **26**, 291 (1978) [*CA* **89**, 128706 (1978)].

<sup>35</sup> R. E. Rondeau, M. A. Berwick, and H. M. Rosenberg, *J. Heterocycl. Chem.* **9**, 427 (1972).

<sup>36</sup> M. Davis, L. W. Deady, and E. Homfeld, *J. Heterocycl. Chem.* **11**, 1011 (1974); *Aust. J. Chem.* **27**, 1221 (1974).

<sup>37</sup> A. Maquestiau, Y. van Haverbeke, R. Flamman, and J. Pierard, *Bull. Soc. Chim. Belg.* **84**, 207 (1975).

<sup>38</sup> Z. Yoshida and T. Kobayashi, *Theor. Chim. Acta* **20**, 216 (1971).

<sup>39</sup> S. D. Sokolov, L. A. Kazitsyna, and I. K. Guseva, *J. Org. Chem. USSR (Engl. Transl.)* **2**, 733 (1966).



studies show that  $pK_a$  values for indoxazene-3-carboxylic acids are comparable to those of *o*-nitrobenzoic acids and emphasize the strong electron-withdrawing effect of the indoxazene nucleus<sup>8</sup> (see also Sections II,C,1 and II,C,2,a).

### C. CHEMICAL PROPERTIES

#### 1. Electrophilic Substitution

A detailed study of the kinetics and mechanism of the nitration of 3-methylindoxazene has been reported.<sup>40</sup> Contrary to earlier findings, nitration in cold concentrated mixed acids furnishes only one product, the 5-nitro derivative. Apparently, nitration of the free base occurs in 80–90% sulfuric acid, whereas at higher acidities the conjugate acid is the species undergoing nitration. Formation of the 5-nitro isomer is in conflict with the theoretical predictions based on the  $\pi$ -electron densities (see Section II,B). This has led the authors to the conclusion that nitration is subject to frontier orbital control rather than charge control.

Indoxazene-3-carboxylic acid and methyl 6-nitroindoxazene-3-carboxylate in mixed acids are nitrated exclusively at the 5-position.<sup>8</sup>

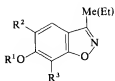
Nitration studies on a series of 3-methyl- and 3-ethylindoxazenes have been recorded.<sup>12</sup> 3-Methyl- and 3-ethylindoxazene yield a mixture of the 5-nitro and 5,7-dinitro derivatives. If the 5-position is blocked (e.g., by chloro or alkyl groups) then, surprisingly, nitration takes place at the 4-position. As expected, the 7-chloro-3-alkyl and the 3,7-dialkyl derivatives are nitrated exclusively at the 5-position, whereas the 3,6-dialkyl and 3-alkyl-6-chloro derivatives yield a mixture of the 5-nitro and 5,7-dinitro compounds. The structures of the nitro compounds were confirmed by <sup>1</sup>H-NMR spectroscopy and, in some instances by synthesis from the nitro-substituted ketoxime acetates (see Section II,A,2).

Bromination of 6-hydroxy-3-alkylindoxazenes in acetic acid at room temperature furnishes the 7-bromo derivatives (**28**;  $R^1 = R^2 = H$ ,  $R^3 = Br$ ) whereas the methoxy compounds (**28**;  $R^1 = Me$ ,  $R^2 = R^3 = H$ ) yield only the 5-bromo derivatives (**28**;  $R^1 = Me$ ,  $R^2 = Br$ ,  $R^3 = H$ ). At 110–120°C the dibromo derivatives (**28**;  $R^1 = H$  or  $Me$ ,  $R^2 = R^3 = Br$ ) are the sole products.<sup>41</sup>

Acylation of indoxazenes are rare events.<sup>1</sup> Of interest, therefore, are reports of the acylation (at the 7-position) of 3-alkyl-6-hydroxyindoxazenes

<sup>40</sup> G. Bianchi, L. Casotti, D. Passadore, and N. Stabile, *J. C. S. Perkin II*, 47 (1977).

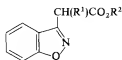
<sup>41</sup> K. A. Thakar, B. M. Bhawal, and A. B. Dumir, *Indian J. Chem.* **18B**, 371 (1979).



(28)



(29)



(30)

under standard Friedel–Crafts conditions.<sup>42</sup> The rearrangement of 6-acetoxy-3-methylindoxazenes to 7-acetyl-6-hydroxy-3-methylindoxazenes (**28**;  $R^1 = R^2 = H$ ,  $R^3 = Ac$ ) in the presence of aluminum chloride at 140°C, represents the first example of a Fries rearrangement in the indoxazene series.<sup>43</sup> Under standard Reimer–Tiemann conditions 6-hydroxy-7-formyl-3-alkylindoxazenes (**28**;  $R^1 = R^2 = H$ ,  $R^3 = CHO$ ) are produced in moderate yield (30–40%) from their 6-hydroxy-3-alkyl derivatives.<sup>44</sup>

2-Ethyl-7-hydroxyindoxazene tetrafluoroborate in boiling sulfuryl chloride yields a monochloro derivative (either the 4- or 6-) in 77% yield.<sup>45</sup> Similarly, sulfonation of the tetrafluoroborate in fuming 30% sulfuric acid affords the zwitterionic 4- or 6-sulfonic acid (**29**) in 90% yield. In contrast, chlorosulfonation of indoxazene at 100°C yields indoxazene-5-sulfonyl chloride (67%).<sup>46</sup>

The electrophilic substitution of indoxazene-3-acetic acid and its derivatives has been investigated extensively. Chlorination with chlorine in acetic acid or with a slight excess of *N*-chlorosuccinimide produces a mixture of the  $\alpha$ -chloroacetic acid (**30**;  $R^1 = Cl$ ,  $R^2 = H$ ) (48.6%) and 3-(dichloromethyl)-indoxazene (5%), whereas with a large excess of *N*-chlorosuccinimide a mixture of 3-(dichloromethyl)- and 3-(trichloromethyl)indoxazene results.<sup>47</sup> Iodination with iodine monochloride in acetic acid, or bromination with an equivalent of bromine in the same medium, yields only the monohalogeno acids (**30**;  $R^2 = H$ ,  $R^1 = I$  and  $Br$ , respectively).<sup>47–49</sup> With an excess of bromine, 3-(tribromomethyl)indoxazene is formed.<sup>48,49</sup> Surprisingly, bromination of the methyl ester (**30**;  $R^1 = H$ ,  $R^2 = Me$ ), even with an excess of

<sup>42</sup> K. A. Thakar and B. M. Bhawal, *J. Indian Chem. Soc.* **54**, 875 (1977).

<sup>43</sup> S. S. Kumari, K. S. R. Krishna Mohan Rao, and N. V. Subba Rao, *Indian J. Chem.* **11**, 541 (1973).

<sup>44</sup> K. A. Thakar and B. M. Bhawal, *Indian J. Chem.* **15B**, 1056 (1977).

<sup>45</sup> D. S. Kemp, S.-W. Wang, R. C. Mollan, S.-L. Hsia, and P. N. Confalone, *Tetrahedron* **30**, 3677 (1974).

<sup>46</sup> D. S. Kemp, *Tetrahedron* **23**, 2001 (1967).

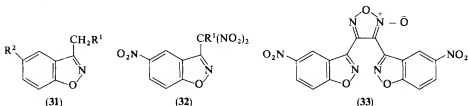
<sup>47</sup> H. Uno and M. Kurokawa, *Chem. Pharm. Bull.* **26**, 3498 (1978).

<sup>48</sup> H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato, and H. Nishimura, *Chem. Pharm. Bull.* **24**, 632 (1976).

<sup>49</sup> M. Giannella, F. Gualtieri, C. Melchiorre, and A. Orlandoni, *Chim. Ther.* **7**, 127 (1972); M. Pignini, M. Giannella, F. Gualtieri, C. Melchiorre, P. Bolle, and L. Angelucci, *Eur. J. Med. Chem.—Chim. Ther.* **10**, 29, 33 (1975).

bromine, affords only the monobromo derivative (**30**;  $R^1 = \text{Br}$ ,  $R^2 = \text{Me}$ ).<sup>48</sup> Careful bromination of the acid with an equivalent of *N*-bromosuccinimide produces a mixture of starting material, the monobromo acid (**30**;  $R^1 = \text{Br}$ ,  $R^2 = \text{H}$ ), 3-(tribromomethyl)indoxazene, and a trace of the  $\alpha,\alpha$ -dibromo acid. Decarboxylation of the reaction mixture gives 2-(dibromomethyl)indoxazene which can be separated from the mono- and tribromomethyl derivatives by thin-layer chromatography.<sup>48</sup> The bromomethyl derivatives have been used to prepare a series of gramine and tryptamine isosteres.<sup>49</sup>

In contrast to halogenation, nitration of indoxazene-3-acetic acid with fuming nitric acid at 0°C furnishes a mixture of nuclear (**31**;  $R^1 = \text{CO}_2\text{H}$ ,  $R^2 = \text{NO}_2$ ) (24%) and side-chain (**32**;  $R^1 = \text{H}$ ) nitration products together with a small amount (9%) of the furoxan **33**.<sup>47</sup> At room temperature a more complex mixture is obtained, consisting of the 5-nitroindoxazene-3-carboxylic acid (24%), the dinitro- and trinitromethyl derivatives (**32**;  $R^1 = \text{H}$  and  $\text{NO}_2$ , respectively), and 6-nitroindoxazene-3-aldehyde (4%). As with bromination, the ester **30** ( $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) and the corresponding 3-acetonitrile behave differently from the parent acid in that nitration yields only the 5-nitro derivatives (**31**;  $R^2 = \text{NO}_2$ ,  $R^1 = \text{CO}_2\text{Me}$  and  $\text{CN}$ , respectively).



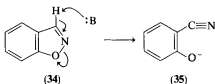
Chlorosulfonation of the acid at 70°C followed by amination yields a mixture of the sulfonamides (**31**;  $R^1 = \text{SO}_2\text{NH}_2$ ,  $R^2 = \text{H}$ ) and (**31**;  $R^1 = R^2 = \text{SO}_2\text{NH}_2$ ). Similar results are obtained with the ester **30** ( $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) and the acetonitrile.

From the results of their studies the authors conclude that the methylene group in indoxazene-3-acetic acid is particularly sensitive to electrophilic substitution, halogenation and sulfonation taking place there in preference to the carbocyclic ring. The reasons for this enhanced reactivity and for the anomalous nitration results are as yet unexplained.<sup>47</sup>

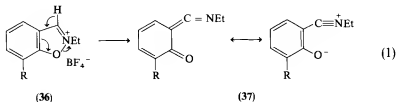
## 2. Ring Fission

a. *By Bases.* The instability of indoxazenes, particularly those unsubstituted at the 3-position, in alkaline solution is well documented.<sup>1</sup> Exhaustive mechanistic studies on the ring opening of 5-, 6-, and 7-substituted

indoxazenes by hydroxide ion and amines reveals that ring cleavage takes place by a concerted  $E_2$  elimination ( $34 \rightarrow 35$ ) and not, as previously thought, by initial loss of the 3-proton.<sup>50</sup>



A similar situation prevails with *N*-ethylindoxazanium salts ( $36$ ) which undergo a facile, general base-catalyzed internal elimination to form the resonance-stabilized and highly electrophilic *N*-ethylbenzoketoketenimine intermediates ( $37$ ) (Eq. 1).<sup>45,46</sup> The reaction of these indoxazanium salts with carboxylate ions to give stable phenolic esters has been developed as a new peptide coupling process, particular use being made of the 7-hydroxy derivative ( $36$ ;  $R = OH$ ).<sup>45</sup> Extensive investigations demonstrate that under optimum conditions (pH 4.5–5.0, with a  $> 0.3 M$  solution of carboxylate ion in aqueous pyridine) peptide esters may be obtained cleanly and efficiently in almost quantitative yields.<sup>51</sup> These coupling reactions parallel those observed with isoxazolium salts.<sup>52</sup>



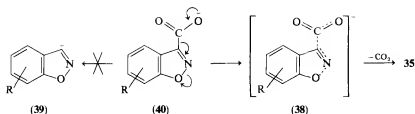
In aqueous solution indoxazene-3-carboxylic acid undergoes slow but quantitative decarboxylation and ring cleavage to *o*-cyanophenol ( $t_{1/2}$  at  $30^\circ C$ , 7 days).<sup>53</sup> From a careful study of substituent and solvent effects on the rate of decarboxylation, and on tritium labeling studies, it is concluded that the reaction involves an intermediateless, concerted loss of carbon dioxide via a transition state conveniently represented as  $38$ , rather than by a stepwise process through carbanion  $39$  (Scheme 3).<sup>8,53</sup>

<sup>50</sup> M. L. Casey, D. S. Kemp, K. G. Paul, and D. D. Cox, *J. Org. Chem.* **38**, 2294 (1973); D. S. Kemp and M. L. Casey, *J. Am. Chem. Soc.* **95**, 6670 (1973).

<sup>51</sup> D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.* **89**, 2743 (1967); D. S. Kemp, *Pept.: Chem. Biochem., Proc. Am. Pept. Symp., 1st*, 1968, 33 (1970); D. S. Kemp, S.-W. Wang, J. Rebek, R. C. Mollan, C. Banquer, and G. Subramanyam, *Tetrahedron* **30**, 3955 (1974); D. S. Kemp, S. J. Wrobel, S.-W. Wang, Z. Bernstein, and J. Rebek, *ibid.*, 3969.

<sup>52</sup> R. B. Woodward and R. A. Olofson, *Tetrahedron, Suppl.* **7**, 415 (1966).

<sup>53</sup> D. S. Kemp and K. Paul, *J. Am. Chem. Soc.* **92**, 2553 (1970).



SCHEME 3

The rates of decarboxylation of substituted indoxazene-3-carboxylic acids correlate well with their  $pK_a$  values, which in turn reflect the electron-withdrawing effects of the substituent groups.<sup>8</sup> 5,6-Dinitroindoxazene-3-carboxylic acid is particularly labile and decarboxylates during recrystallization or on storage.

The rate of decarboxylation of 6-nitroindoxazene-3-carboxylic acid is subject to dramatic solvent effects which support the anionic nature of the transition state (38).<sup>8,53</sup> The marked acceleration on going from water (rate  $7.3 \times 10^{-6} \text{ sec}^{-1}$ ) to a dipolar aprotic solvent (e.g., dimethylformamide, rate  $3.7 \times 10 \text{ sec}^{-1}$ ) is interpreted in terms of the different solvation requirements of the carboxylate anion (40), with its comparatively localized charge, and the transition state (38) with its delocalized charge. In protic solvents intermolecular hydrogen bonding with the carboxylate ion inhibits decarboxylation by selectively stabilizing the acid, whereas dipolar aprotic solvents stabilize the transition state (38) and hence accelerate loss of carbon dioxide.

As anticipated, the strong intramolecular hydrogen bonding present in the 4-hydroxy-3-carboxylic acid (40;  $R = 4\text{-OH}$ ) inhibits conversion to the salicylonitrile in all solvent systems.<sup>8</sup> A similar but less marked effect is noticed with the zwitterionic 4-pyridinium derivative (41) in which there is electrostatic stabilization.<sup>54</sup>

Bunton and his co-workers<sup>55</sup> have shown that the decarboxylative ring opening of 6-nitroindoxazene-3-carboxylic acid is strongly catalyzed by cationic micelles and by micelles of zwitterionic surfactants such as *N,N*-dimethyl-*N*-dodecylglycine. Later studies by other workers indicate that the decarboxylation is also catalyzed by polysoaps,<sup>56</sup> modified polyethyleneimines,<sup>57</sup> cycloheptaamylose,<sup>9</sup> and by poly(vinylbenzo-18-crown-6).<sup>58</sup> The

<sup>54</sup> D. S. Kemp, J. Reczek, and F. Vellaccio, *Tetrahedron Lett.*, 741 (1978).

<sup>55</sup> C. A. Bunton, M. Minch, and L. Sepulveda, *J. Phys. Chem.* **75**, 2707 (1971); C. A. Bunton, M. J. Minch, J. Hidalgo, and L. Sepulveda, *J. Am. Chem. Soc.* **95**, 3262 (1973); C. A. Bunton, A. A. Kamego, M. J. Minch, and J. L. Wright, *J. Org. Chem.* **40**, 1321 (1975).

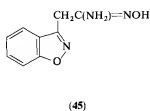
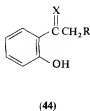
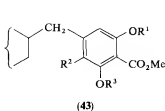
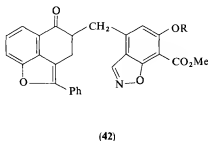
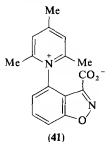
<sup>56</sup> T. Kunitake, S. Shinkai, and S. Hirotsu, *J. Org. Chem.* **42**, 306 (1977).

<sup>57</sup> J. Suh, I. S. Scarpa, and I. M. Klotz, *J. Am. Chem. Soc.* **98**, 7060 (1976).

<sup>58</sup> S. C. Shah and J. Smid, *J. Am. Chem. Soc.* **100**, 1426 (1978).

last reagent is particularly effective in conjunction with cesium chloride; at 5°C a rate increase of 86,000 relative to that in water is noted.

b. *By Reduction.* Reduction of the 5-acetoxyindoxazene-4-carboxylate **42** ( $R = \text{Ac}$ ), a tetracycline precursor, with palladium charcoal and hydrogen in a mixture of acetic acid and dimethylformamide yields the hydroxy-aldehyde **43** ( $R^1 = \text{Ac}$ ,  $R^2 = \text{CHO}$ ,  $R^3 = \text{H}$ ), whereas under similar conditions the phenol **42** ( $R = \text{H}$ ) furnishes the hydroxynitrile **43** ( $R^1 = R^3 = \text{H}$ ,  $R^2 = \text{CN}$ ).<sup>59</sup>



Indoxazene-3-acetic acid with palladium charcoal and hydrogen undergoes reductive ring opening to the imine (**44**;  $X = \text{NH}$ ,  $R = \text{CO}_2\text{H}$ ), which in acetic acid hydrolyzes to the hydroxy- $\beta$ -ketoacid (**44**;  $X = \text{O}$ ,  $R = \text{CO}_2\text{H}$ ).<sup>20</sup> 3-Hydroxyindoxazenes are cleaved by sodium borohydride at 80°C to *o*-hydroxybenzamides.<sup>23</sup> In contrast, 3-(*o*-aminophenyl)indoxazene with lithium aluminum hydride undergoes ring transformation to 3-(*o*-hydroxyphenyl)indazole<sup>29</sup> (see Section II,C,4). Catalytic reduction (palladium charcoal in ethanol) of indoxazene-3-acetamidoxime (**45**), a new potent psychotropic agent,<sup>60</sup> yields either the iminoamidoxime [**44**;  $X = \text{NH}$ ,

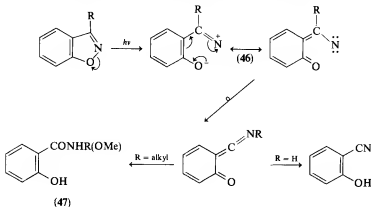
<sup>59</sup> E. Aufderhaar, J. E. Baldwin, D. H. R. Barton, D. J. Faulkner, and M. Slaytor, *J. Chem. Soc. C*, 2175 (1971).

<sup>60</sup> M. Shimizu, K. Yoshida, T. Karasawa, M. Masuda, M. Oka, T. Ito, C. Kamei, M. Hori, Y. Sohji, and K. Furukawa, *Experientia* **30**, 405 (1974); T. Karasawa, K. Furukawa, K. Yoshida, and M. Shimizu, *Chem. Pharm. Bull.* **24**, 2673 (1976); T. Ito, K. Yoshida, and M. Shimizu, *ibid.*, 2918; T. Yamaguchi, Y. Utsui, and M. Hashimoto, *J. Chromatogr.* **150**, 147 (1978).

$R = C(NH_2)=NOH]$  or the ketoamidine [44;  $X = O$ ,  $R = C(NH_2)=NH]$ , depending on the quantity of hydrogen used.<sup>61</sup> Indoxazene-3-acetonitrile, the precursor of (45), is reduced under similar conditions to the iminonitrile (44;  $X = NH$ ,  $R = CN$ ).

c. *By Photolysis.* Photolysis, in diglyme, of indoxazenes unsubstituted at position 3 affords mixtures of the isomeric benzoxazoles and *o*-hydroxybenzonitriles, the former generally as the major products.<sup>62</sup> Quenching experiments indicate that the hydroxynitriles are formed directly from the indoxazenes via the triplet manifold, whereas benzoxazole formation is a more complex process involving the excited singlet state and *o*-hydroxyisonitrile intermediates<sup>63</sup> (see Section II,C,4).

Subsequent studies demonstrated, however, that these photoinduced ring fissions are remarkably solvent-dependent. For example, in water or methanol virtually quantitative yields of benzoxazoles are obtained, whereas with a low concentration of water or methanol in acetonitrile (or hexane), 3-substituted indoxazenes yield only *o*-hydroxyamides and -esters; indoxazene itself gives salicylonitrile.<sup>64</sup> These transformations are rationalized in terms of ring cleavage of the indoxazene to the polar (or nitrenoid) intermediate (46), which by rearrangement gives either benzoxazoles (see Section II,C,4) or, as outlined in Scheme 4, the salicylic acid derivatives (47).



SCHEME 4

Photolysis of indoxazene in 96% sulfuric acid produces a mixture of 2,5-dihydroxy- (64%) and 2,3-dihydroxybenzaldehyde (17%); 3-methyl-

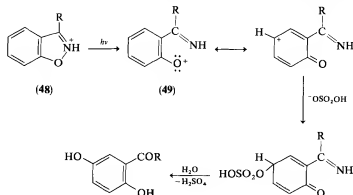
<sup>61</sup> H. Ito, M. Kurokawa, and H. Nishimura, *Chem. Pharm. Bull.* **24**, 644 (1976).

<sup>62</sup> H. Göth and H. Schmid, *Chimia* **20**, 148 (1966).

<sup>63</sup> J. P. Ferris and F. R. Antonucci, *J. Am. Chem. Soc.* **96**, 2010, 2014 (1974); J. P. Ferris, F. R. Antonucci, and R. W. Trimmer, *ibid.*, **95**, 919 (1973).

<sup>64</sup> W. Heinzelmann and M. Märky, *Helv. Chim. Acta* **57**, 376 (1974).

indoxazene yields the corresponding dihydroxyacetophenones.<sup>65</sup> Ultraviolet spectroscopic studies reveal that in 96% sulfuric acid indoxazenes are protonated at nitrogen, and hence it is deduced that ring opening involves heterolysis of the N—O bond of the excited, singlet-state indoxazanium cations (48). The singlet ground-state oxenium ions (49) thus formed then undergo conjugate addition of bisulfate ion followed by hydrolysis to a mixture of phenols as exemplified in Scheme 5 for the 2,5-dihydroxy product.



SCHEME 5

Irradiation of 3-methylindoxazene in dilute sulfuric acid produces only *o*-aminophenol, supposedly by photoisomerization to the 2-methylbenzoxazole and then hydrolysis.<sup>65</sup>

### 3. Reactions of Substituents

a. *Hydroxy Groups.* Information on the tautomeric nature of 3-hydroxyindoxazenes is scarce.<sup>66</sup> Infrared studies indicate that in the solid state the parent system exists solely as the enol tautomer whereas in chloroform solution both keto and enol forms are present.<sup>67</sup>

Methylation with methyl iodide<sup>23,67</sup> or diazomethane<sup>67</sup> produces a mixture of the 3-methoxy derivatives and *N*-methyl-1,2-benzisoxazolin-3-ones. In contrast, acetylation with acetic anhydride yields only the *O*-acetyl derivatives.<sup>23</sup> Subsequent acylation studies, however, reveal a much more complex pattern of behavior.<sup>68</sup> In the majority of cases ultraviolet,

<sup>65</sup> M. Georgarakis, T. Doppler, M. Märky, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 2916 (1971); T. Doppler, H. Schmid, and H.-J. Hansen, *ibid.* **62**, 314 (1979).

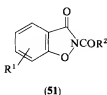
<sup>66</sup> J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem., Suppl.* **1**, 308 (1976).

<sup>67</sup> L. J. Darlage, T. H. Kinstle, and C. L. McIntosh, *J. Org. Chem.* **36**, 1088 (1971).

<sup>68</sup> H. Böshagen and W. Geiger, *Chem. Ber.* **103**, 123 (1970); **102**, 3775 (1969).



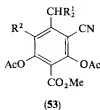
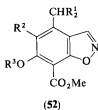
infrared, and proton magnetic resonance spectroscopic data show that the *O*-acyl derivatives (50) are the only products. However, on gentle heating (125°C) they rearrange to *N*-acylbenzisoxazolinones (51). Under more vigorous conditions (225°C) irreversible rearrangement to the isomeric *N*-acylbenzoxazolinones takes place (see Section II.C.4). Some of the *N*-alkoxycarbonyl derivatives, in particular the 5-bromo compound (51;  $R^1 = \text{Br}$ ,  $R^2 = \text{OEt}$ ), display intense central nervous system depressant activity.<sup>69</sup>



Alkylation of 3-hydroxyindoxazenes in dimethylformamide in the presence of potassium carbonate with alkyl bromides,  $\alpha$ -bromoesters and -ketones, and with propargyl bromides affords mainly the *O*-alkyl derivatives.<sup>70</sup> The *N*-alkyl isomers are also formed, but in most cases undergo base-catalyzed rearrangement to 1,3-benzoxazin-4-ones (see Section II.C.4).

Phosphorus oxychloride in triethylamine at 140–150°C converts 3-hydroxyindoxazenes into their 3-chloro derivatives in excellent yields.<sup>71</sup>

Acetylation of the highly substituted 6-hydroxyindoxazene 52 ( $R^1 = \text{H}$ ,  $R^2 = \text{NO}_2$ ,  $R^3 = \text{H}$ ) in acetic anhydride with sulfuric acid as catalyst proceeds normally to give the acetate (52;  $R^1 = \text{H}$ ,  $R^2 = \text{NO}_2$ ,  $R^3 = \text{Ac}$ ), whereas with acetic anhydride and sodium acetate ring cleavage to the cyanodiacetate (53;  $R^1 = \text{H}$ ,  $R^2 = \text{NO}_2$ ) is the favored process.<sup>13</sup>



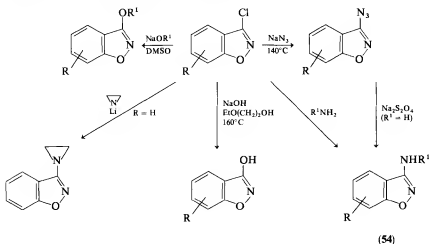
Aryloxyacetic acids obtained by treating 6-hydroxy-7-acylindoxazenes with ethyl bromoacetate cyclize in acetic anhydride–sodium acetate to furo[6,7-*d*]-1,2-benzisoxazoles.<sup>42</sup>

<sup>69</sup> E. Domagalina and T. Slawik, *Pol. J. Pharmacol. Pharm.* **30**, 717 (1978); K. Kolasa, *Acta Pol. Pharm.* **36**, 241 (1979).

<sup>70</sup> H. Uno and M. Kurokawa, *Chem. Pharm. Bull.* **26**, 549 (1978).

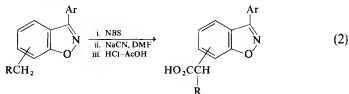
<sup>71</sup> H. Böshagen, *Chem. Ber.* **100**, 3326 (1967).

b. *Halogeno Groups.* 3-Chloroindoxazenes are highly susceptible to nucleophilic substitution and are useful precursors of other 3-substituted indoxazenes as exemplified in Scheme 6.<sup>71,72</sup>



SCHEME 6

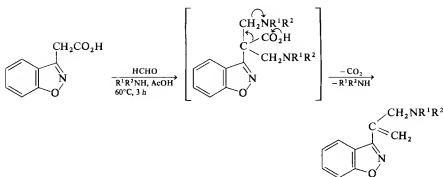
c. *Alkyl Groups.* Attempts to oxidize the 4-methyl-5-nitroindoxazene (**52**;  $R^1 = R^3 = H$ ,  $R^2 = NO_2$ ) to the corresponding carboxylic acid were unsuccessful.<sup>13</sup> However, Thiele oxidation of the related acetyl derivative (**52**;  $R^1 = R^2 = H$ ,  $R^3 = Ac$ ) produces the gem-diacetate (**52**;  $R^1 = OAc$ ,  $R^2 = H$ ,  $R^3 = Ac$ ) in 30% yield, which on acetylation with acetic anhydride-sodium acetate gives the nitrile (**53**;  $R^1 = OAc$ ,  $R^2 = H$ ), a useful tetracycline ring A precursor. A series of 3-arylindoxazene-5-, -6-, and -7- acetic and -propanoic acids possessing antiinflammatory activity, have been prepared by the sequence of reactions noted in Eq. (2).<sup>11</sup>



The enhanced reactivity toward electrophilic substitution of the methylene group in indoxazene-3-acetic acids, noted in Section II.C.1, is again prominent during the Mannich reaction (Scheme 7).<sup>73</sup>

<sup>72</sup> C. F. Laureri and E. Gaetini, *Boll. Soc. Ital. Biol. Sper.* **48**, 297 (1972) [*CA* **77**, 126487 (1972)].

<sup>73</sup> H. Uno and M. Kurokawa, *Chem. Pharm. Bull.* **26**, 312 (1978).



SCHEME 7

3-Methyl- and 3-(bromomethyl)indoxazenes are inert under the conditions used to brominate indoxazene-3-carboxylic acid (Section II,C,1).<sup>48</sup>

A large number of stilbenes derived from 3-(*p*-tolyl)indoxazene have been prepared and their fluorescence spectra measured.<sup>74</sup>

d. *Nitro Groups*. Reduction of methyl 4-nitroindoxazene-3-carboxylate with stannous chloride in 12 *N* hydrochloric acid affords the 4-amino derivative.<sup>8</sup> Stannous chloride in acetic acid effects reduction of 3-(*p*-cyanophenyl)-5-nitroindoxazene to the amine unaccompanied by reduction or hydrolysis of the resident cyano group.<sup>3</sup>

e. *Amino Groups*. 5-Amino-3-(*p*-cyanophenyl)indoxazene yields the 5-cyano derivative by normal Sandmeyer reaction.<sup>3</sup> Methyl 4-hydroxyindoxazene-3-carboxylate is accessible from the 4-amino compound by treating the diazonium sulfate with cupric nitrate and cuprous oxide in sulfuric acid.<sup>8</sup>

3-Aminoindoxazene differs from related 3-aminobenzodiazoles in that it undergoes nonregiospecific cycloaddition of methyl propiolate to give a mixture of 2-oxo-2*H*-pyrimido- and 4-oxo-4*H*-pyrimido[1,2-*b*]benzisoxazole.<sup>75</sup>

f. *Acyl Groups*. Modification of the acyl groups in 7-acyl-6-hydroxy-3-alkylindoxazenes provides access to a variety of fused benzisoxazolo heterocycles including isoxazolo[4,3-*a*]flavonols,<sup>76</sup>  $\gamma$ -pyrano-,<sup>43,44</sup> furo[2,3-*g*]-, and isoxazolo[5,4-*e*]benzisoxazoles.<sup>42</sup>

<sup>74</sup> H. Berger and A. E. Siegrist, *Helv. Chim. Acta* **62**, 779 (1979); R. B. Palmberg and A. E. Siegrist, *ibid.*, 1816; B. F. S. E. de Sousa and A. E. Siegrist, *ibid.*, **61**, 2904 (1978).

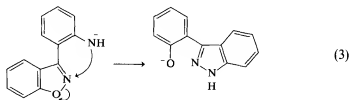
<sup>75</sup> H. Reimlinger, M. A. Peiren, and R. Merényi, *Chem. Ber.* **105**, 794 (1972).

<sup>76</sup> E. V. S. Bhushan Rao, K. S. R. Krishna Mohan Rao, and N. V. Subba Rao, *Curr. Sci.* **42**, 498 (1973).

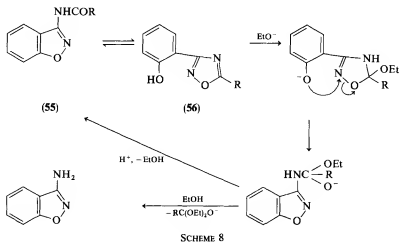
#### 4. Ring Transformations

Ring transformations of indoxazenes have been effected under acidic, basic, thermal, and photolytic conditions.

As mentioned in Section II,C,2,b, attempts to reduce 3-(*o*-aminophenyl)-indoxazene with lithium aluminum hydride result in rearrangement to 3-(*o*-hydroxyphenyl)indazole. The rearrangement is equally successful with sodium hydride in boiling tetrahydrofuran and proceeds via the amine anion as shown in Eq. (3).<sup>29</sup>

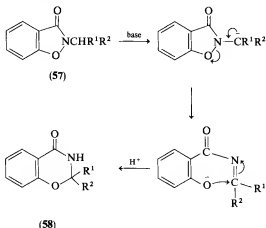


The base-induced interconversion of 3-acylaminoindoxazenes (**55**) and 3-(2-hydroxyphenyl)-1,2,4-oxadiazoles (**56**), first reported by Lindemann and Cissé,<sup>1</sup> is dependent on the nature of the acyl group (COR) and the base.<sup>77</sup> In sodium hydroxide the acetyl and benzoyl derivatives (**55**; R = Me or Ph) exist predominantly as the oxadiazoles (**56**), whereas in excess sodium ethoxide hydrolysis of the acyl group by the intramolecular process outlined in Scheme 8 becomes important.



<sup>77</sup> K. Harsányi, *J. Heterocycl. Chem.* **10**, 957 (1973).

2-Substituted 1,3-benzoxazin-4-ones (**58**) are isolated as by-products (2–25%) from the alkylation of 1,2-benzisoxazolin-3-ones in dimethylformamide<sup>70</sup> (see also Section II,C,3,a). The ring expansion occurs via proton loss from the *N*-alkyl-1,2-benzisoxazolin-3-one (**57**) (Scheme 9) and is facilitated by electron-withdrawing groups (i.e.,  $R = \text{CO}_2\text{Et}$ , Ph, CPh, or  $\text{C}\equiv\text{CH}$ ). Alkylation with allyl bromide yields only the *O*-allyl (51%) and *N*-allyl (45%) indoxazenes.



SCHEME 9

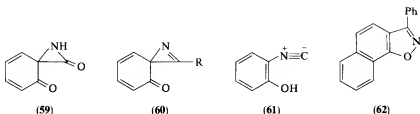
A Lössén-type rearrangement via an acylnitrenium ion (see Scheme 1) is thought to be responsible for the acid-catalyzed isomerization of 2-aryl-1,2-benzisoxazolin-3-ones to 3-arylbenzoxazolin-2-ones.<sup>25</sup> 3-Acyloxyindoxazenes and *N*-acyl-1,2-benzisoxazolin-3-ones on thermolysis (225°C) or photolysis rearrange to *N*-acylbenzoxazolin-2-ones (see Section II,C,3,a). The *N*- and *O*-allyl derivatives behave similarly.<sup>68</sup> Exceptionally, rearrangement of the 3-alkoxycarbonyl compounds (**51**;  $R = O\text{-alkyl}$ ) is accompanied by loss of carbon dioxide and formation of *N*-alkylbenzoxazolinones.

The thermal rearrangement of 3-hydroxyindoxazene to benzoxazolin-2-one is temperature-dependent. The indoxazene is inert at 250°C but rearranges quantitatively at 450°C.<sup>78</sup> 3-Phenylindoxazene under flash vacuum pyrolysis conditions (800°C, 0.1–1 torr) rearranges to 3-phenylbenzoxazole in 80% yield.<sup>79</sup> In both reactions a spiroazirine intermediate [**59** or **60** ( $R = \text{Ph}$ )], analogous to those isolated in some isoxazole–oxazole rearrangements,<sup>80</sup> is considered likely.

<sup>78</sup> T. H. Kinstle and L. J. Darlage, *J. Heterocycl. Chem.* **6**, 123 (1969).

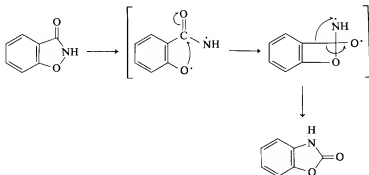
<sup>79</sup> K. L. Davies, R. C. Storr, and P. J. Whittle, *J. C. S. Chem. Commun.*, 9 (1978).

<sup>80</sup> B. J. Wakefield and D. J. Wright, *Adv. Heterocycl. Chem.* **25**, 148 (1979).



Spiroazirine intermediates also figure prominently in the photorearrangements of indoxazenes to benzoxazoles and *o*-cyanophenols<sup>62,63</sup> (see also Section II.C,2,c). Low-temperature ( $-77^{\circ}\text{C}$ ) infrared and ultraviolet studies show that benzoxazole arises by cyclization of the *o*-hydroxyisocyanide intermediate **61**.<sup>63</sup> Interest has since centered on attempts to detect possible precursors of the isocyanide. Early efforts to find likely species such as the polar intermediate **46** ( $\text{R} = \text{H}$ ) (or its radical equivalent) or the spiroazirine **60** ( $\text{R} = \text{H}$ ) failed.<sup>63</sup> Later investigations showed that these photorearrangements are dependent on the nature of the 3-substituent ( $\text{R}$ ) and the solvent.<sup>64,81</sup> In nonpolar solvents various products including *o*-cyanophenols and benzoxazoles are produced depending on the nature of  $\text{R}$ , whereas in polar aprotic solvents benzoxazoles are formed exclusively.<sup>81</sup> Subsequent low-temperature infrared, ultraviolet, and flash-photolysis studies provide evidence for azirine intermediates, and in certain cases (e.g., the condensed isoxazole **62**) the azirines are reasonably stable.

3-Hydroxyindoxazenes undergo analogous rearrangements to benzoxazolin-2-ones.<sup>67</sup> However, sensitization studies support a rearrangement from the triplet state; and these results, coupled with low-temperature spectroscopic data, which fail to detect any aziridone or *o*-hydroxyaryl isocyanate intermediates, lead the authors to propose a radical mechanism (Scheme 10)



SCHEME 10

<sup>81</sup> K. H. Grelmann and E. Tauer, *J. Photochem.* **6**, 365 (1977).

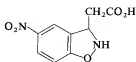
as the most likely reaction pathway. The photostability of 3-methoxyindoxazene supports the view that homolysis of the keto rather than the enol tautomer is responsible for initiating the rearrangement.

An oxygen-dependent photodimerization of indoxazene to bis(2,2'-benzoxazole) has been reported.<sup>82</sup>

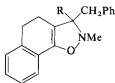
## D. REDUCED DERIVATIVES

### 1. Dihydroindoxazenes

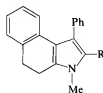
6-Nitrocoumarin and hydroxylamine in ethanol yield a 1:2 adduct (**20**) (see Section II.A,3) which with mineral acid cyclizes to 5-nitro-2,3-dihydroindoxazene-3-acetic acid (**63**).<sup>21</sup> With diazomethane, **63** yields the methyl ester and with acetic anhydride the *N*-acetyl derivative. Oxidation to indoxazene-3-carboxylic acid is successful using selenium dioxide, whereas hydrogenation in the presence of palladium-charcoal brings about ring opening to  $\beta$ -amino- $\beta$ -(2-hydroxy-5-nitrophenyl)propanoic acid.



(63)



(64)



(65)

*N*-Ethylindoxazanium tetrafluoroborate adds benzyl magnesium chloride to yield 3-benzyl-2-ethyl-2,3-dihydroindoxazene which, on reduction with Raney nickel and hydrogen, ring-opens to *N*-ethyl-1-(*o*-hydroxyphenyl)-2-phenethylamine.<sup>83</sup> The corresponding 2-alkyl-3-benzyl-2,3-dihydro compounds (**64**; R = H or Me), derived from 4,5-dihydronaphtho[2,1-*d*]isoxazolium perchlorates, on heating rearrange, possibly via 2-acylaziridine intermediates, to naphthopyrroles (**65**). Indoles, however, are not formed from 2,3-dihydroindoxazenes.

2,3-Dihydroindoxazenes are available in almost quantitative yields by 1,3-dipolar cycloadditions of nitrones to benzyne.<sup>84</sup>

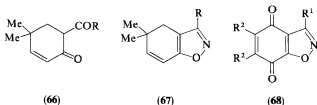
6-Acylcyclohex-2-en-1-ones (**66**; R = H, Me, or CH=CHAr) with hydroxylamine hydrochloride in acetic acid afford 4,5-dihydroindoxazenes

<sup>82</sup> K. H. Grellmann and E. Tauer, *Tetrahedron Lett.*, 375 (1974).

<sup>83</sup> I. Adachi, K. Hirada, R. Miyaki, and H. Kano, *Chem. Pharm. Bull.*, **22**, 61 (1974).

<sup>84</sup> H. Seidl, R. Huisgen, and R. Knorr, *Chem. Ber.*, **102**, 904 (1969).

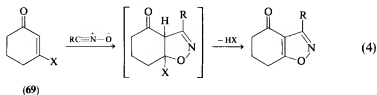
(67).<sup>85,86</sup> 4,7-Dioxindoxazenes (**68**;  $R^1$  = aryl or heteroaryl,  $R^3$  = alkyl), formed by 1,3-dipolar cycloaddition of the appropriate nitrile oxide to a 1,4-benzoquinone, have bactericidal and fungicidal properties.<sup>87</sup> Apparently, optimum yields of **68** are obtained by generating the nitrile oxide *in situ* from the hydroxamoyl chloride.



## 2. Tetrahydroindoxazenes

The 4,5,6,7-tetrahydro derivatives are formally 4,5-disubstituted isoxazoles, the chemistry of which has recently been reviewed in Volume 25 of this series.<sup>80</sup> Accordingly, in this section only selected aspects of their chemistry are mentioned along with the chemistry of the other less common, isomeric tetrahydroindoxazenes.

1,3-Dipolar cycloaddition of nitrile oxides to cyclohexenes and the action of hydroxylamine on 2-acylcyclohexanones constitute the main synthetic routes to 4,5,6,7-tetrahydroindoxazenes. A convenient one-step synthesis utilizes the addition of a nitrile oxide to cyclohexenones of type **69** ( $X$  = OH, OMe, OAc, Cl,  $NH_2$ , or  $NR_2$ ) (Eq. 4).<sup>88</sup>



Cycloaddition of benzonitrile *N*-oxide and cyclohexa-1,3-diene produces a mixture of 3a,4,5,7a-tetrahydroindoxazene (**70**), the bis-adducts **71** ( $R$  = H)

<sup>85</sup> M. A. Elkasaby, *Indian J. Chem.* **15B**, 690 (1977).

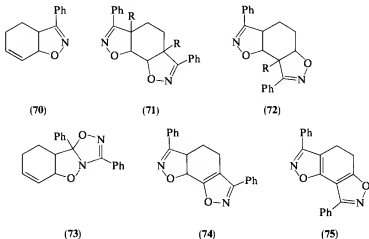
<sup>86</sup> P. Margaretha, *Helv. Chim. Acta* **58**, 929 (1975).

<sup>87</sup> T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **41**, 2206 (1968); H. Kano, M. Ogata, and Y. Watanabe, Japan Kokai 72/42,659 [*CA* **78**, 97623 (1973)]; Japan Kokai 72/43,336; [*CA* **78**, 132686 (1973)].

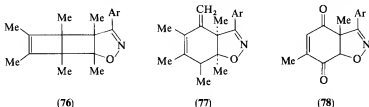
<sup>88</sup> A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and A. G. Pozdeyev, *Synthesis*, 43 (1978); A. A. Akhrem, V. A. Khripach, and F. A. Lakhvich, *Chem. Heterocycl. Compd. (Engl. Transl.)* **10**, 784 (1974).



and **72** ( $R = H$ ) and diadduct **73**, this last product being formed by a secondary addition of the nitrile oxide to **70**.<sup>89</sup> Adducts **71** and **72** ( $R = H$ ) with *N*-bromosuccinimide yield the bromo derivatives **71** and **72** ( $R = Br$ ), which with triethylamine are dehydrobrominated to the dihydro and tetrahydro derivatives **74** and **75**, respectively. The tetrahydroindoxazene **70** is oxidized directly by *N*-bromosuccinimide to 3-phenylindoxazene.



Polymethyl 3a,4,7,7a-tetrahydroindoxazenes (**77**) are obtained by thermal rearrangement of the benzonitrile oxide-hexamethyl-Dewar-benzene cycloadducts (**76**).<sup>90</sup> Reaction of 2,4,6-trimethylbenzonitrile oxide with 3,6-dimethyl-*p*-benzoquinone yields the 4,7-dioxo-3a,4,7,7a-tetrahydroindoxazene **78** ( $Ar = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$ ) or its regioisomer, and addition proceeds similarly with 2,6-dimethyl-*p*-benzoquinone. In a number of other examples, nitrile oxides were found to cycloadd to the  $\text{C}=\text{O}$  bond of quinones.<sup>91</sup>



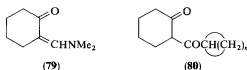
The action of hydroxylamine hydrochloride on 2-acylcyclohexanones and their derivatives in ethanolic pyridine frequently produces a mixture of

<sup>89</sup> G. F. Bettinetti and A. Gamba, *Gazz. Chim. Ital.* **100**, 1144 (1970).

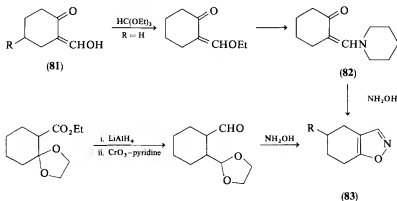
<sup>90</sup> G. Brüntrup and M. Christl, *Tetrahedron Lett.*, 3369 (1973).

<sup>91</sup> S. Shiraishi, S. Ikeuchi, M. Senô, and T. Asahara, *Bull. Chem. Soc. Jpn.* **51**, 921 (1978).

isomeric 4,5,6,7-tetrahydro-1,2- and -2,1-benzisoxazoles, the latter generally as the major products.<sup>92</sup> One notable exception is the ketoenamine **79**, which gives 4,5,6,7-tetrahydroindoxazene in 90% yield. 2-(Cycloalkanoyl)cyclohexanones (**80**;  $n = 2, 3, 4$ , or 5) under the above conditions give tetrahydroanthranils except when  $n = 3$ , in which case a mixture of 3-cyclobutyl-tetrahydro-1,2- and -2,1-benzisoxazole is formed.<sup>92</sup>



The mixture of isomeric tetrahydrobenzisoxazoles produced by condensing *o*-formylcyclohexanone with hydroxylamine has proved to be extremely difficult to separate. Consequently, two specific syntheses of 4,5,6,7-tetrahydroindoxazene (**83**) have been developed independently and are outlined in Scheme 11.<sup>93,94</sup> The latter reaction sequence has also been used to prepare pure 3-methyl-4,5,6,7-tetrahydroindoxazene.<sup>94</sup> The *t*-butylcyclohexanone **81** ( $R = t\text{-Bu}$ ) condenses with hydroxylamine to give the *t*-butyltetrahydroindoxazene **83** ( $R = t\text{-Bu}$ ) in 81% yield.<sup>95</sup> It is worth noting that the morpholino analog of enamine **82** with hydroxylamine gives a 4:1 mixture of tetrahydro-2,1- and -1,2-benzisoxazoles.<sup>92</sup>



SCHEME 11

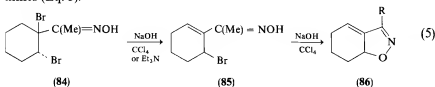
<sup>92</sup> R. Jacquier, C. Petrus, F. Petrus, and M. Valentin, *Bull. Soc. Chim. Fr.*, 2665,2678 (1970).

<sup>93</sup> R. A. Olofson and Y. L. Marino, *Tetrahedron* **26**, 1779 (1970).

<sup>94</sup> J. P. Ferris and R. W. Trimmer, *J. Org. Chem.* **41**, 13 (1976).

<sup>95</sup> M. E. Kuehne, *J. Org. Chem.* **35**, 171 (1970).

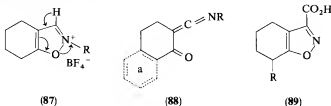
3-Methyl-5,6,7,7a-tetrahydroindoxazene (**86**; R = Me) has been prepared by base-induced cyclization of either the di- (**84**) or monobromo (**85**) ketoximes (Eq. 5).<sup>96</sup>



An anomalous result is obtained on condensing 3-bromo-2-cyanocyclohexene with hydroxyurea in that 3-amino-5,6,7,7a-tetrahydroindoxazene (**86**; R = NH<sub>2</sub>) is produced rather than the expected 3-amino-4,5,6,7-tetrahydro compound.<sup>97</sup>

The photoisomerization of 4,5,6,7-tetrahydroindoxazenes to 4,5,6,7-tetrahydrobenzoxazoles appears to involve spiroazirine—2-isocyanocyclohexanone—intermediates analogous to those discussed in Section II.C.4.<sup>63,94</sup>

N-Alkyl-4,5,6,7-tetrahydroindoxazanium tetrafluoroborates (**87**; R = Me or Et), like the fully unsaturated systems, are easily ring-opened by nucleophiles. For example, triethylamine in methylene dichloride generates the moderately stable iminoketenes (**88**).<sup>93</sup> The angular fused analog (**88a**; R = Et) is isolable as a stable oil.



4,5,6,7-Tetrahydroindoxazene-3-carboxylic acids (**89**) are transformed into 3-amino-2-phenyl-4,5,6,7-tetrahydroindazoles by boiling phenylhydrazine.<sup>98</sup> On reduction with hydrogen and Raney nickel in ethanol, the acid hydrazides of **89** undergo ring opening to the imines **90** followed by cyclization to 4-amino-5,6,7,8-tetrahydrocinnolin-3-ones.<sup>99</sup> The phenylhydrazone of 3-benzoyl-4,5,6,7-tetrahydroindoxazene behaves similarly.<sup>100</sup>

N-Allyl-4,5,6,7-tetrahydro-1,2-benzisoxazolin-3-one and oxalyl chloride yield 2-allyl-3-chloro-4,5,6,7-tetrahydroindoxazanium chloride.<sup>101</sup>

<sup>96</sup> K. P. Park, C.-Y. Shiue, and L. B. Clapp, *J. Org. Chem.* **35**, 2065 (1970).

<sup>97</sup> W. Klötzer, H. Breitschneider, E. Fitz, R. Reiner, and G. Bader, *Monatsh. Chem.* **101**, 1109 (1970).

<sup>98</sup> M. Ruccia, N. Vivona, and F. Piozzi, *Gazz. Chim. Ital.* **97**, 1494 (1967).

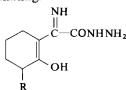
<sup>99</sup> M. Ruccia, N. Vivona, S. Plescia, and V. Sprio, *J. Heterocycl. Chem.* **8**, 289 (1971).

<sup>100</sup> V. Sprio, O. Migliara, and S. Plescia, *Ann. Chim. (Rome)* **61**, 648 (1971).

<sup>101</sup> K. Tomita, S. Sugai, T. Kobayashi, and T. Murakami, *Chem. Pharm. Bull.* **27**, 2398 (1979).

## 3. Hexahydroindoxazenes

Contrary to earlier reports,<sup>1</sup> 3a,4,5,6,7,7a-hexahydroindoxazenes can be prepared by cycloaddition of nitrile oxides to cyclohexene.<sup>102,103</sup> Similar cycloadditions with 1,2-dihydronaphthalene produce a mixture of the regioisomers **91a** and **91b**, and with cyclohex-2-en-1-one a mixture of 3-aryl-4-oxo- and 3-aryl-7-oxo-3a,4,5,6,7,7a-hexahydroindoxazenes, the former predominating.<sup>104</sup>



(90)



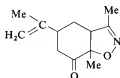
(91)

4-Oxo-3a,4,5,6,7,7a-hexahydroindoxazenes (**92**) are oxidized by chloranil to the 4,5,6,7-tetrahydro derivatives and are useful precursors for the synthesis of 2-acylcyclohexane-1,3-diones and for glutarimide antibiotic analogs.<sup>105</sup>

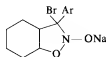
Acetonitrile oxide and 3-methyl-6-(2-prop-1-enyl)cyclohexene yield only an exocyclic adduct, whereas with carvone a 1.7:1 mixture of the exocyclic adduct and the hexahydro-1,2-indoxazene (**93**) is produced.<sup>106</sup> 1-Cyano-cyclohexene and hydroxyurea in the presence of alkoxide give 3-amino-3a,4,5,6,7,7a-hexahydroindoxazene, albeit in low yield (10%).<sup>107</sup>



(92)



(93)



(94)

Thermolysis of the sodium salts of (bromonitromethyl)benzenes at 90°–110°C in the presence of cyclohexene fails to yield any products indicative of carbene intermediates, but rather 3-aryl-3a,4,5,6,7,7a-hexahydroindoxazenes

<sup>102</sup> T. Sasaki and T. Yoshioka, *Bull. Chem. Soc. Jpn.* **40**, 2604 (1967); H. Dahn, B. Favre, and J.-P. Leresche, *Helv. Chim. Acta* **56**, 457 (1973).

<sup>103</sup> K. Bast, M. Christ, R. Huisgen, W. Mack, and R. Sustmann, *Chem. Ber.* **106**, 3258 (1973).

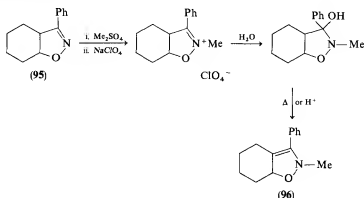
<sup>104</sup> G. Bianchi, C. de Micheli, R. Gandolfi, P. Grünanger, P. V. Finza, and O. V. de Pava, *J. C. S. Perkin I*, 1148 (1973); G. Bianchi, C. de Micheli, and R. Gandolfi, *ibid.*, 1518 (1976).

<sup>105</sup> A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, *Chem. Heterocycl. Comd. (Engl. Transl.)* **11**, 285 (1975); **15**, 194 (1979).

<sup>106</sup> C.-Y. Shive, R. G. Lawler, and L. B. Clapp, *J. Org. Chem.* **41**, 2210 (1976).

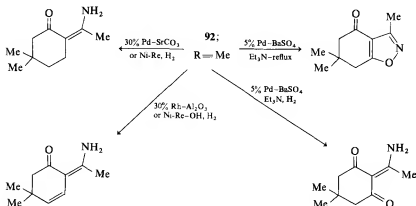
<sup>107</sup> J.-L. Olive, C. Petrus, and F. Petrus, *Bull. Soc. Chim. Fr.*, 1138 (1973).

in moderate (15–35%) yields.<sup>108</sup> This reaction is explained in terms of a cycloaddition of the sodium salt of the *aci*-nitro tautomer to cyclohexene followed by loss of sodium hypobromite from the resulting adduct (**94**). Conversion of 3a,4,5,6,7,7a-hexahydroindoxazenes into 2H-4,5,6,7,7a-hexahydroindoxazenes (**96**) can be effected by the reaction sequence outlined in Scheme 12.<sup>109</sup>



SCHEME 12

Catalytic hydrogenation/dehydrogenation of the hexahydroindoxazene **92** ( $\text{R} = \text{Me}$ ) has been studied in detail; results are summarized in Scheme 13.<sup>110</sup>



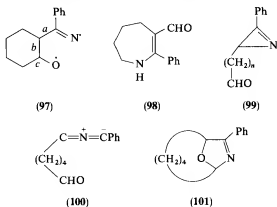
SCHEME 13

<sup>108</sup> N. Alexandrou, E. Coutouli, and A. Varvoglis, *Tetrahedron Lett.*, 2131 (1975).

<sup>109</sup> A. Belly, C. Petrus, and F. Petrus, *Bull. Soc. Chim. Fr.*, 1390 (1973); 1025 (1974).

<sup>110</sup> A. A. Akhrem, F. A. Lakhvich, V. A. Khrpach, and I. I. Petrusovich, *Chem. Heterocycl. Comd. (Engl. Transl.)* **12**, 742 (1976).

3-Phenyl-3a,4,5,6,7,7a-hexahydroindoxazine (**95**) undergoes an intriguing photorearrangement and fragmentation which has been rationalized in terms of selective bond cleavage and rearrangement of the initially formed biradical intermediate **97**.<sup>111</sup> Benzonitrile (9% yield) results from cleavage of the exocyclic C—C bond (*a*), whereas homolysis of bond (*b*) yields a new biradical, recyclization of which accounts for the enamino aldehyde **98**. A similar homolytic fission of bond (*c*) followed by ring closure yields azirine **99** (*n* = 4) (isolable when *n* = 2) which, by a photoinduced ring opening to the dipolar intermediate **100** followed by an intramolecular 1,3-dipolar cycloaddition, yields 2,5-tetramethylene- $\Delta^3$ -isoxazoline (**101**) (27%). Azirines (**99**) are of particular interest as the acyclic analogs of the elusive spiroazirine intermediates proposed in the photoisomerizations of indoxazenes and their tetrahydro derivatives (see Sections II,C,4 and II,D,2).



#### 4. Octahydroindoxazenes

Fully reduced indoxazenes are best prepared by 1,3-dipolar cycloaddition of nitrones to cyclohexenes<sup>112</sup> and to cyclohexanone enamines.<sup>113–115</sup>

One of several products from the reaction of tetranitromethane with cyclohexene has been reformulated as the dinitrooctahydroindoxazine **102** (*R* = H).<sup>116</sup> This rather complex reaction has been reinvestigated in detail

<sup>111</sup> O. Seshimoto, T. Kumagi, K. Shimizu, and T. Mukai, *Chem. Lett.*, 1195 (1977).

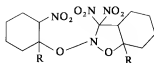
<sup>112</sup> R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.* **101**, 2043, 2568 (1968).

<sup>113</sup> Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Jpn.* **40**, 1740 (1967); **43**, 1913, 3002 (1970).

<sup>114</sup> O. Tsuge, M. Tashiro, and Y. Nishihara, *Nippon Kagaku Zasshi* **92**, 72 (1971).

<sup>115</sup> N. Singh and K. Krishan, *Indian J. Chem.* **11**, 1076 (1973).

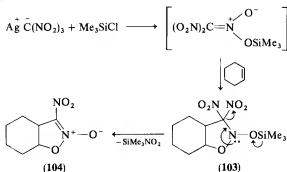
<sup>116</sup> K. Torssell, *Acta Chem. Scand.* **21**, 1392 (1967).



(102)

by Soviet workers who find it to be general for 1-substituted cyclohexenes.<sup>117</sup> For example, 1-methylcyclohexene and tetranitromethane in ether (5 days) afford the dimethyl compound (102; R = Me) in 76% yield.

The 3,3-dinitrooctahydroindoxazene 103, prepared as indicated in Scheme 14, readily loses nitrotrimethylsilane to give the *N*-oxide 104.<sup>118</sup> This *N*-oxide is also one of the products from the action of bromotrinotromethane on cyclohexene.<sup>116</sup>



SCHEME 14

## E. USES

Indoxazene-3-acetic acid derivatives, analogous to the 3-acetamidoxime (45) noted in Section II,C,2,b, have been found to possess antidepressant and hypotensive activity and are the subjects of numerous Japanese patents.<sup>119</sup>

<sup>117</sup> K. V. Altukhov, E. V. Ratsino, and V. V. Perekalin, *J. Org. Chem. USSR (Engl. Transl.)* **9**, 267 (1973); V. A. Buevich, K. V. Altukhov, and V. V. Perekalin, *ibid.* **6**, 184 (1970); **7**, 1425 (1971).

<sup>118</sup> S. L. Ioffe, L. M. Makarenkova, M. V. Kashutina, V. A. Tartakovskii, N. N. Rozhdestvenskaya, L. I. Kovalenko, and V. G. Isagulyants, *J. Org. Chem. USSR (Engl. Transl.)* **9**, 931 (1973).

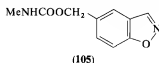
<sup>119</sup> H. Nishimura, M. Shimizu, H. Uno, T. Hirooka, Y. Masuda, and M. Kurokawa, Japan Kokai 75/29, 555 [*CA* **83**, 131574 (1975)]; Japan Kokai 75/52,054 [*CA* **83**, 193286 (1975)]; Japan Kokai 74/116,055 [*CA* **83**, 28210 (1975)]; Japan Kokai 74/116,054 [*CA* **83**, 28211 (1975)]; Japan Kokai 75/52,057 [*CA* **83**, 193287 (1975)]; Japan Kokai 75/52,055 [*CA* **83**, 193,285 (1975)]; Japan Kokai 75/50,371 [*CA* **83**, 206232 (1975)]; Japan Kokai 74/116,057 [*CA* **83**, 116057 (1975)]; Japan Kokai 74/116,056 [*CA* **83**, 10038 (1975)]; Japan Kokai 75/50,368 [*CA* **84**, 17316 (1976)]; Japan Kokai 75/50,367 [*CA* **83**, 206234 (1975)].

In addition, 3-(sulfamoylmethyl)indoxazenes and their derivatives show promise as anticonvulsants.<sup>120</sup>

In rats, orally administered 3-hydroxyindoxazene displays superior anti-inflammatory and antipyretic activity to salicylamide and paracetamol, respectively.<sup>121</sup> A wide range of 3-substituted indoxazenes have antibacterial and antifungal properties,<sup>122</sup> while insecticidal and acaricidal activity is prominent in a large number of 1,2-benzisoxazolyl-3-phosphates, -phosphorothioates, and -phosphonothioates.<sup>123</sup>

Cyanine and merocyanine dyes based on the indoxazene nucleus are useful photographic sensitizers.<sup>124</sup>

The 5-substituted indoxazene (**105**) is a new protective group for peptide synthesis and withstands most peptide manipulations including trifluoroacetic acid.<sup>125</sup> It is, however, cleaved by hydrogenolysis, by hydrogen bromide in acetic acid, and by a novel two-step sequence involving an aprotic base in a dipolar aprotic solvent followed by solvolysis at pH 7.



The  $\beta$ -chloroethylamine derivative (**54**;  $R = H$ ,  $R^1 = CH_2CH_2Cl$ ) is active in 1% concentration in reducing the emergence of adult common houseflies.<sup>72</sup>

Of the reduced indoxazenes, attention is drawn to the hydrazide of 4,5,6,7-tetrahydroindoxazene-3-carboxylic acid which, as the hydrochloride, is more potent than iproniazid as an inhibitor of mitochondrial monoamine oxidase.<sup>126</sup>

Other uses of reduced indoxazenes include the antibacterial and antiprotozoal activity of 3-(5-nitro-2-furyl)-3a,4,5,6,7,7a-hexahydro derivatives,<sup>127</sup>

<sup>120</sup> H. Uno, M. Kurokawa, Y. Masuda, and H. Nishimura, *J. Med. Chem.*, **22**, 180 (1979).

<sup>121</sup> M. Impicciatore, T. Vitali, and G. Bertaccini, *Boll. Soc. Ital. Biol. Sper.*, **47**, 296 (1971) [*CA* **76**, 254 (1972)]; *Pharmacol. Res. Commun.*, **3**, 385 (1971) [*CA* **77**, 70117 (1972)].

<sup>122</sup> H. Uno, M. Kurokawa, M. Shimizu, Y. Takase, and K. K. Natsuka, Japan Kokai 74/70,963 [*CA* **81**, 136133 (1974)]; B. M. Bhawal, G. V. Umalkar, D. S. Mukadam, and K. A. Thakar, *Marathwada Univ. J. Sci.: Nat. Sci.*, **16**, 7 (1977) [*CA* **89**, 100772 (1978)].

<sup>123</sup> W. Lorenz, H. Böshagen, I. Hammann, W. Behrenz, and B. Homeyer, Ger. Offen. 2,031,750 (1972) [*CA* **76**, 99640 (1972)]; Ger. Offen. 2,458,626 (1976) [*CA* **85**, 118002 (1976)]; Ger. Offen. 2,515,793 (1976) [*CA* **86**, 106563 (1977)]; Ger. Offen. 2,544,551 (1977) [*CA* **87**, 39462 (1977)].

<sup>124</sup> A. Sato, A. Ogawa, K. Shiba, and Y. Nakamura, Ger. Offen. 2,534,500 (1976) [*CA* **85**, 184808 (1976)]; S. Ikenoue, T. Masuda, A. Ogawa, and A. Sato, Japan Kokai 76/27,924; [*CA* **85**, 151797 (1976)]; M. Hanata, H. Takei, A. Sato, and A. Ogawa, Ger. Offen. 2,547,533 (1976) [*CA* **86**, 36313 (1977)].

<sup>125</sup> D. S. Kemp and C. F. Hoyng, *Tetrahedron Lett.*, 4625 (1975).

<sup>126</sup> A. Kurosawa, *Chem. Pharm. Bull.*, **17**, 36, 43, 49 (1969).

<sup>127</sup> S. Minami, J. Matsumoto, M. Shimizu, and Y. Takase, U.S. Patent 3,631,169 (1971) [*CA* **76**, 140776 (1972)]; British Patent 1,162,257 (1969) [*CA* **72**, 12709 (1970)].



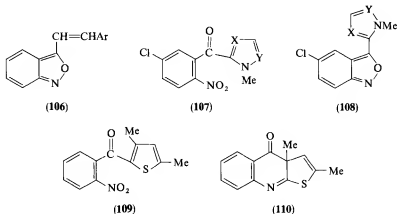
and the trypanocidal properties of some 3-(2-nitroimidazolyl)-4,5,6,7-tetrahydro compounds.<sup>128</sup>

### III. Anthranils (2,1-Benzisoxazoles)

#### A. PREPARATION

##### 1. From *o*-Nitro and *o*-Nitroso Compounds

a. *By Reduction of o-Nitroacylbenzenes.* A useful method of preparing anthranils is due to Cadogan and his co-workers who, during their comprehensive investigations into the synthetic uses of trivalent phosphorus compounds,<sup>129</sup> found that *o*-nitroacylbenzenes undergo reductive cyclization to anthranils.<sup>130</sup> 5-Chloro-2-nitroacetophenone and *o*-nitrochalcone furnish 5-chloro-3-methyl- and 3-( $\beta$ -styryl)- (106; Ar = Ph) anthranil, respectively, in practicable yields. *o*-Nitroacetophenone, however, yields *N*-(2-acetylphenyl)phosphoramidate as the sole isolable product, although PMR studies on the crude reaction mixture indicate the presence ( $\sim 9\%$ ) of 3-methylanthranil. The reaction fails with ethyl *o*-nitrobenzoate—ethyl anthranilate (14%), (*N*-*o*-ethoxycarbonyl)phosphoramidate (11%), and its *N*-ethyl derivative (15.5%) being the only products.



<sup>128</sup> P. Kulsa and C. Rooney, U.S. Patent 3,915,978 (1975) [CA 84, 59471 (1976)]; U.S. Patent 4,010,176 (1977) [CA 87, 23279 (1977)].

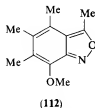
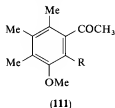
<sup>129</sup> J. I. G. Cadogan, in "Organophosphorus Reagents in Organic Synthesis" (J. I. G. Cadogan, ed.), p. 269. Academic Press, New York, 1979.

<sup>130</sup> J. I. G. Cadogan, R. Marshall, D. M. Smith, and M. J. Todd, J. Chem. Soc. C, 2441 (1970).

The *o*-nitrobenzoylimidazole and -pyrazole **107**; (X = N, Y = CH and X = CH, Y = N) with triethyl phosphite in ethanol cyclize normally to the respective 3-heteroarylthranils (**108**).<sup>131</sup> The (nitrobenzoyl)thiophene **109**, however, yields not the anthranil but the isomeric thieno[3,2-*b*]quinolone (**110**)<sup>132</sup> (see Section II,C,5,a).

Anthranil and its 3-methyl derivative are obtained by electrolytic reduction of *o*-nitrobenzaldehyde and *o*-nitroacetophenone, respectively.<sup>133</sup> In each case the anthranils are characterized as their HgCl<sub>2</sub> complexes.

Reductive cyclization of *o*-nitrophenacyl bromide with zinc and ammonium chloride is accompanied by dehalogenation; 3-methylanthranil and a little 2-aminoacetophenone are the only products.<sup>134</sup> Stannous chloride and hydrochloric acid at room temperature is a popular mixture for reducing *o*-nitroacetophenones to 3-methylanthranils.<sup>135</sup> Generally, however, under reflux conditions further reduction to the *o*-aminoacetophenone results. The nitroketone **111** (R = NO<sub>2</sub>) with palladium charcoal and hydrogen, sodium bisulfite, or cold stannous chloride and hydrochloric acid yields anthranil **112**, whereas with the last reagents at 100°C, the aminoketone (**111**; R = NH<sub>2</sub>) is obtained, although in variable yield.<sup>136</sup>



Reductive cyclization of polychloro-*o*-nitrobenzaldehydes and nonafluoro-*o*-nitrobenzophenone with tin and acetic acid and stannous chloride and hydrochloric acid, respectively, proceed without hydrodehalogenation.<sup>137,138</sup> 3-Aminoanthranil is obtained, albeit in low yield (17%), by electrolytic reduction of *o*-nitrobenzonitrile.<sup>139</sup>

<sup>131</sup> R. Y. Ning, J. F. Blount, P. B. Madan, and R. I. Fryer, *J. Org. Chem.* **42**, 1791 (1977).

<sup>132</sup> O. Meth-Cohn, *Heterocycles*, **14**, 1497 (1980).

<sup>133</sup> M. Le Guyader and M. Le Demezet, *C. R. Acad. Sci., Ser. C* **259**, 4719 (1964); M. Le Guyader, *ibid.* **262**, 1383 (1966).

<sup>134</sup> M. Kawana, M. Yoshioka, S. Miyaji, H. Kataoka, Y. Omote, and N. Sugiyama, *Nippon Kagaku Zasshi* **86**, 526 (1965).

<sup>135</sup> H. du Crocq, R. J. J. C. Lousberg, and C. A. Saleminck, *Recl. Trav. Chim. Pays-Bas* **93**, 139 (1974).

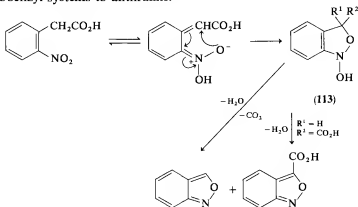
<sup>136</sup> T. Tokoroyama, S. Maeda, T. Nishikawa, and T. Kubota, *Tetrahedron* **25**, 1047 (1969); *Tetrahedron Lett.*, 745 (1967); T. Tokoroyama and T. Kubota, *Tetrahedron* **26**, 1085 (1970).

<sup>137</sup> R. C. Bertelson and W. J. Becker, *J. Heterocycl. Chem.*, **3**, 422 (1966).

<sup>138</sup> C. M. Jenkins, A. E. Pedler, and J. C. Tatlow, *Tetrahedron* **27**, 2557 (1971).

<sup>139</sup> M. Jubault and D. Peltier, *Bull. Soc. Chim. Fr.*, 2365 (1972).

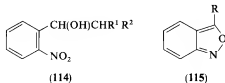
b. *From o-Nitrobenzyl Compounds.* A general mechanistic rationale (exemplified in Scheme 15), involving *aci*-nitro tautomers, has been proposed to explain the thermal, and acid- and base-catalyzed rearrangements of 2-nitrobenzyl systems to anthranils.<sup>140</sup>



SCHEME 15

The photoconversion of 2,2'-dinitrodiphenylmethanes to 3-(*o*-nitrophenyl)anthranils in ethanolic sulfuric acid proceeds via a similar reaction pathway, the acid promoting dehydration of the dihydroanthranil intermediate **113** ( $R^1 = H$ ,  $R^2 = o\text{-NO}_2\text{C}_6\text{H}_4$ ).<sup>141</sup> However, in the absence of acid an intramolecular redox reaction, leading ultimately to dibenzodiazepinone *N*-oxides and acridones, becomes the major process.

*o*-Nitrobenzyl alcohols (**114**;  $R^1 = H$ ,  $R^2 = \text{Ar}$ ) undergo related acid-catalyzed rearrangements to mixtures of 2-arylisatogens and 3-benzoylanthranils (**115**;  $R = \text{COAr}$ ).<sup>142</sup> *cis*- and *trans*-Stilbenes are also formed by direct dehydration of the alcohol. *o*-Nitrotolan in acid solution gives a similar mixture of products, and not just 2-phenylisatogen as was reported previously.



Thermolysis of 2,3,4,5,6-pentafluoro-2'-nitrodiphenylmethanol in liquid paraffin at 165°C yields 3-(pentafluorophenyl)anthranil.<sup>143</sup> A similar reac-

<sup>140</sup> D. R. Eckroth and T. G. Cochran, *J. Chem. Soc. C*, 2660 (1970).

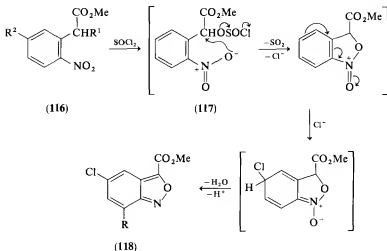
<sup>141</sup> C. P. Joshua and P. K. Ramdas, *Tetrahedron Lett.*, 4359 (1974); *Aust. J. Chem.* **29**, 865 (1976).

<sup>142</sup> J. M. Bakke, *Acta Chem. Scand.* **29B**, 667 (1975); *ibid.*, 1063.

<sup>143</sup> P. L. Coe, A. E. Jukes, and J. C. Tatlow, *J. Chem. Soc. C*, 2020 (1966).

tion takes place on heating the alcohol in 70% sulfuric acid, or on heating its *p*-toluenesulfonate derivative in toluene.

A 1:4 mixture of methyl *o*-nitromandelate (**116**;  $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ) and thionyl chloride at room temperature yields not the expected  $\alpha$ -chloro compound (**116**;  $R^1 = \text{Cl}$ ,  $R^2 = \text{H}$ ), but the 5-chloroanthranil-3-carboxylate (**118**;  $R = \text{H}$ ).<sup>144</sup> Reaction conditions are, however, critical; for example, neat thionyl chloride at room temperature produces only the sulfite ester of **116**, whereas in pyridine at  $-80^\circ\text{C}$  the  $\alpha$ -chloro compound (**116**;  $R^1 = \text{Cl}$ ,  $R^2 = \text{H}$ ) is obtained. The chloromandelate (**116**;  $R^1 = \text{OH}$ ,  $R^2 = \text{Cl}$ ) is inert to boiling thionyl chloride, but on prolonged (12 h) treatment with thionyl chloride in chloroform it yields the dichloroanthranil **118** ( $R = \text{Cl}$ ). A mechanistic rationale (Scheme 16) involving the sulfinyl chloride **117** is proposed.



SCHEME 16

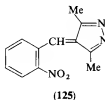
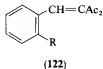
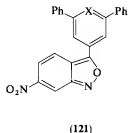
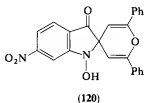
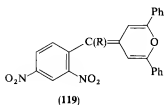
Anthranil is a minor product from the electrolytic reduction of the erythro or threo forms of the *o*-nitrobenzyl alcohol **114** ( $R^1 = \text{Me}$ ,  $R^2 = \text{NO}_2$ ).<sup>145</sup> The fluorosulfonic acid-induced cyclization of (*o*-nitrophenyl)succinic anhydride affords a mixture of 4-hydroxy-2-quinolone and anthranil-3-acetic acid (**115**;  $R = \text{CH}_2\text{CO}_2\text{H}$ ), and not, as previously reported, a mixture of 1-hydroxyindole- and 2-hydroxy- $\Delta^2$ -indoline-3-carboxylic acids.<sup>146</sup>

<sup>144</sup> T. J. McCord, D. R. Smith, J. K. Swan, A. M. Goebel, D. E. Thornton, C. C. Yakshe, and A. L. Davis, *J. Heterocycl. Chem.* **16**, 1249 (1979).

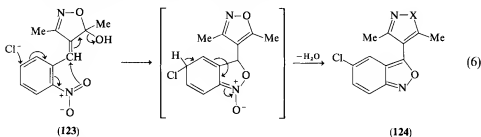
<sup>145</sup> H. Lund and N. H. Nilsson, *Acta Chem. Scand.* **30B**, 5 (1976).

<sup>146</sup> R. M. Acheson, R. G. Bolton, and I. Hunter, *J. Chem. Soc. C*, 1067 (1970).

c. *From o-Nitrobenzylidene Compounds.* The *o*-nitrobenzylidene-pyran **119** ( $R = H$ ), formed by condensing 2,4-dinitrotoluene with 2,6-diphenyl-4-methoxypyrylium perchlorate, undergoes phototransformation to the spiropyranindoline **120**, which on treatment with perchloric acid rearranges to the explosive 3-(4-pyrylium)anthranil perchlorate **121** ( $X = O^+ClO_4^-$ ).<sup>147</sup> In aqueous pyridine this anthranil ring-opens to a 1,5-diketone, cyclization of which with ammonia yields the pyridylanthranil **121** ( $X = N$ ). Similar reactions occur with the cyano derivatives **119** ( $R = CN$ ).<sup>148</sup>



Unsaturated  $\beta$ -diketones (e.g. **122**;  $R = H$ ) and hydroxylamine generally yield isoxazoles. However, the nitro derivative (**122**;  $R = NO_2$ ) with hydroxylamine in acetonitrile or acetic acid at 50°C yields the chloroisoxazoloanthranil **124** ( $X = O$ ) by nucleophilic substitution and cyclization of the initially formed isoxazoline **123** as outlined in Eq. (6).<sup>149</sup>



An analogous cyclization is observed on treating 4-(*o*-nitrobenzylidene)-3,5-dimethylisopyrazoles, e.g. **125**, with acyl halides in pyridine. 3-(1-Acyl-3,

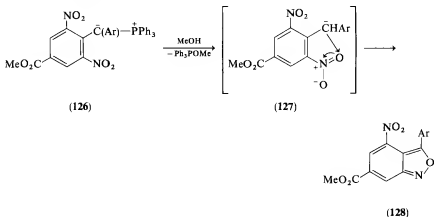
<sup>147</sup> J. A. van Allan, S. Farid, G. A. Reynolds, and S. Chie Chang, *J. Org. Chem.* **38**, 2834 (1973).

<sup>148</sup> J. A. van Allan and G. A. Reynolds, *J. Heterocycl. Chem.* **11**, 395 (1974).

<sup>149</sup> T. Kurihara, T. Sakaguchi, and H. Hirano, *J. Heterocycl. Chem.* **13**, 661 (1976).

5-dimethylpyrazolo)anthranils (e.g. **124**; X = NCOR) are obtained in high yields (58–92%).<sup>150</sup>

Methanolysis, followed by intramolecular cyclization of the anion **127** onto the adjacent nitro group is thought to be responsible for the conversion of the Wittig reagent **126** into the anthranil **128** (Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>).<sup>151</sup>



d. *From o-Nitrosoacylbenzenes.* Deoxygenative cyclization of *o*-nitrosoacylbenzenes with trivalent phosphorus compounds takes place under much milder conditions than the corresponding nitro compounds.<sup>129</sup> Hitherto, however, the inaccessibility of suitable *o*-nitroso compounds has severely limited their synthetic usefulness. Welcome, therefore, is the development of a synthesis of *o*-nitrosopropiophenones by acid-catalyzed isomerization of *o*-nitrocyclopropylbenzenes (**129**) which permits the synthesis of 3-ethylanthranils (**131**; R<sup>1</sup> = H, Et, *t*-Bu, Br, Ac, or NO<sub>2</sub>, R<sup>2</sup> = H) under mild conditions (e.g., triphenylphosphine in benzene or ethanol at room temperature).<sup>152</sup>

Subsequent studies reveal that excellent yields (70–95%) of 3-ethylanthranils are also obtained by reducing the *o*-nitrosopropiophenones with warm sodium bisulfite solution.<sup>153</sup> With dry hydrogen chloride in an inert solvent (e.g., benzene) ring closure of **130** (R<sup>1</sup> = R<sup>2</sup> = H) is accompanied by

<sup>150</sup> T. Kurihara, Y. Sakamoto, T. Sakaguchi, and H. Hirano, *Chem. Pharm. Bull.* **26**, 1141 (1978); T. Kurihara, T. Sakaguchi, and H. Hirano, *ibid.* **24**, 1106 (1976).

<sup>151</sup> S. L. Tripp, F. B. Block, and G. Barile, *J. Med. Chem.* **16**, 60 (1973).

<sup>152</sup> Yu. S. Shabarov, S. S. Mochalov, A. N. Fedotov, and V. V. Kalashnikov, *Khim. Geterotsikl. Soedin.*, 1195 (1975).

<sup>153</sup> A. N. Fedotov, S. S. Mochalov, and Yu. S. Shabarov, *Zh. Prikl. Khim. (Leningrad)* **50**, 1860 (1977) [*CA* **87**, 201000 (1977)]; USSR Patent 529, 161 (1976) [*CA* **86**, 55418 (1977)]; S. S. Mochalov, T. S. Oretskaya, V. V. Karpova, and Yu. S. Shabarov, *Zh. Org. Khim.* **13**, 836 (1977).



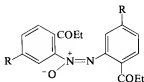
(129)



(130)



(131)



(132)

nuclear chlorination (5- and 7-positions) in a manner analogous to that outlined in Scheme 16.<sup>154</sup> In methanolic hydrogen chloride, however, the reaction is much more complex. In addition to the 5- and 7-chloroanthranils, 5-methoxy-3-ethylanthranil, 3-ethylanthranil, *o*-nitro- and *o*-aminopropiophenone, and the azoxy compound (132; R = H) are also formed.<sup>155</sup> A corresponding mixture of products is obtained with hydrogen bromide in benzene.

In concentrated sulfuric acid at 30–35°C, the dicyclopropyldinitrobenzene **129** (R<sup>1</sup> = cyclopropyl, R<sup>2</sup> = NO<sub>2</sub>) yields anthranil **131** (R<sup>1</sup> = cyclopropyl; R<sup>2</sup> = NO<sub>2</sub>) directly, albeit in low yield (5–7%).<sup>156</sup> In contrast to sulfuric acid, which attacks the dicyclopropylnitrobenzene **129** (R<sup>1</sup> = cyclopropyl, R<sup>2</sup> = H) at the cyclopropane ring adjacent to the nitro group, mercuric acetate in boiling methanol effects ring opening of the other cyclopropyl unit.<sup>157</sup> Sequential treatment of the mercury compound **129** [R<sup>1</sup> = CH(OMe)CH<sub>2</sub>CH<sub>2</sub>HgCl, R<sup>2</sup> = H] so formed with bromine and chloroform, then concentrated sulfuric acid at –20°C, yields the nitroso-propiophenone, reductive cyclization of which, with sodium bisulfite in chloroform, furnishes anthranil **131** [R<sup>1</sup> = CH(OMe)CH<sub>2</sub>CH<sub>2</sub>Br, R<sup>2</sup> = H] in the 58% yield.

Later studies demonstrate that the *o*-nitrosopropiophenones (130) cyclize exothermally in the presence of an equimolar amount of phenylhydrazine

<sup>154</sup> Yu. S. Shabarov and S. S. Mochalov, *Khim. Geterotsikl. Soedin.*, 1334 (1973); USSR Patent, 367,099 (1973); [CA 79, 5324 (1973)].

<sup>155</sup> S. S. Mochalov, T. P. Surikova, and Yu. S. Shabarov, *Khim. Geterotsikl. Soedin.*, 886,1334 (1976).

<sup>156</sup> S. S. Mochalov, S. A. Ermishkina, S. K. Erglis, and Yu. S. Shabarov, *J. Org. Chem. USSR (Engl. Transl.)*, 11, 1409 (1975).

<sup>157</sup> Yu. S. Shabarov, S. S. Mochalov, T. S. Oretskaya, and V. V. Karpova, *J. Organomet. Chem.*, 150, 7 (1978).

in toluene to give a mixture of 3-ethylantranils (**131**) and the azoxy compounds (**132**).<sup>158</sup> With an excess of phenylhydrazine the latter become the major products.

Thermal disproportionation of 3,5-di-*t*-butyl-2-nitrosotoluene in boiling benzene produces a mixture of 5,7-di-*t*-butylantranil and the aminotoluene.<sup>159</sup> The corresponding di-*t*-butylnitrotoluene remains unchanged even under harsh conditions (in methanol, sealed tube at 110°C for 9 days). Cyclization of the nitroso compounds becomes more rapid as the nitroso group becomes more sterically crowded. For example, the *o*-nitrosoethyl analog cyclizes to the anthranil at 5°C, whereas the isopropyl derivative is unstable.

e. *From o-Nitrotoluenes.* 4,6-Dinitroanthranil has been isolated in low yield (2–4%) as one of the products from the photolysis, and controlled thermal decomposition, of 2,4,6-trinitrotoluene.<sup>160</sup>

Reinvestigation of the base-catalyzed rearrangement of *o*-nitrotoluene to anthranilic acid using <sup>18</sup>O-enriched water has confirmed anthranil as a reaction intermediate.<sup>161</sup> Anthranil is also suspected as being an intermediate in the gas-phase conversion of *o*-nitrotoluene to anthranilic acid.<sup>162</sup> 4-*t*-Butyl-7-methyl-6-nitro- and 6-*t*-butyl-5-methoxy-4-nitroanthranil are secondary photoproducts of 2-methoxy-4-methyl-3,5-dinitro-*t*-butylbenzene ("musk ambrette") in methanolic sodium hydroxide.<sup>163</sup>

Warm (70°C) fuming sulfuric acid (60%) converts 2,5-dichloro-3,6-dimethyl-1,4-dinitrobenzene into 4,7-dichloro-6-methyl-5-nitroanthranil in moderate yield.<sup>164</sup>

f. *From o-Nitrobenzaldehydes and Aromatic Compounds.* The preparation of 3-arylantranils by the reaction of 2-nitro- and 2,4-dinitrobenzaldehydes with benzene derivatives in the presence, generally, of strong acid has been extended to include methoxy- (previously thought to be inert)<sup>1</sup>

<sup>158</sup> S. S. Mochalov, A. N. Fedotov, and Yu. S. Shabarov, *J. Org. Chem. USSR (Engl. Transl.)* **15**, 847 (1979).

<sup>159</sup> R. Okazaki, M. Watanabe, Y. Inagaki, and N. Inamoto, *Tetrahedron Lett.*, 3439 (1978); T. Hosogai, N. Inamoto, and R. Okazaki, *J. Chem. Soc. C*, 3399 (1971).

<sup>160</sup> J. C. Dacons, H. G. Adolph, and M. J. Kamlet, *J. Phys. Chem.* **74**, 3035 (1970); N. E. Burlingson, L. A. Kaplan, and C. E. Adams, *U.S. N. T. I. S., AD Rep. AD-769670/IGA* (1973) [*CA* **80**, 85370 (1974)].

<sup>161</sup> P. Willadsen, B. Zerner, and C. G. MacDonald, *J. Org. Chem.* **38**, 3411 (1973).

<sup>162</sup> J. Bakke, H. Heikman, and G. Nyström, *Acta Chem. Scand.* **26**, 355 (1972).

<sup>163</sup> D. Döpp, U. Arfsten-Romberg, W. Bolz, W. van Hoof, and H. Kosfeld, *Chem. Ber.* **112**, 3946 (1979).

<sup>164</sup> N. S. Dokunikhin and S. A. Sokolov, *Zh. Vses. Khim. O-va* **17**, 695 (1972) [*CA* **78**, 58284 (1973)]; *Tezisy Vses. Simp. Org. Sint.: Benzoidnye Aromat. Soedin.*, 1st, 1974, 43 (1974) [*CA* **87**, 22598 (1977)].

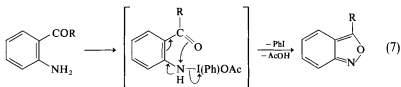


and dimethoxybenzenes<sup>165</sup> and aniline.<sup>166</sup> The reaction with aniline, which is useful for the direct synthesis of 3-(*p*-aminophenyl)anthranils, is carried out in the presence of phosphorus oxychloride and is accompanied by nuclear halogenation at the 5-position. The mechanism of these complex reactions, which hitherto have been assumed to involve anthranil *N*-oxide intermediates<sup>1,167</sup> (Section III,E), awaits clarification.

## 2. From *o*-Amino Compounds

Oxidative cyclization of *o*-aminoacylbenzenes is a much less common process for the synthesis of anthranils than the reductive cyclizations discussed in the previous section, mainly because the *o*-aminoketones are in many instances best prepared by reductive ring opening of anthranils (see Section III,C,3). Nevertheless, a few examples have been recorded. Oxidation of *o*-aminobenzophenones to the nitroketones using peroxytrifluoroacetic acid, permaleic acid, or persulfuric acid proceed via the 3-phenylanthranil which occasionally is isolable.<sup>168</sup> Caro's acid is also a useful oxidant.<sup>169</sup>

A novel and highly successful oxidizing agent is phenyl iodosoacetate [PhI(OAc)<sub>2</sub>]. In benzene solution, this easily prepared reagent oxidizes 2-formyl-, 2-acetyl-, and 2-benzoylaniline to anthranil and its 3-methyl and 3-phenyl derivatives in 21, 71, and 81% yield, respectively.<sup>170</sup> Evidence has been accumulated to show that the first stage in the oxidation consists of nucleophilic displacement of acetate followed by neighboring group participation of the acyl function as outlined in Eq. (7).



In contrast, oxidation of *o*-aminobenzophenone with lead tetraacetate under a variety of conditions yields only azo compound.<sup>171</sup> However, the

<sup>165</sup> M. Ionescu and I. Hopartean, *Stud. Univ. Babes-Bolyai, Ser. Chem.* **17**, 69 (1972) [*CA* **78**, 97255 (1973)]; **16**, 117 (1971) [*CA* **76**, 33897 (1972)]; **15**, 67 and 77 (1970) [*CA* **73**, 130863 (1970)]; I. Panea, I. Hopartean, and M. Ionescu, *ibid.* **19**, 30 (1974) [*CA* **83**, 96984 (1975)].

<sup>166</sup> J. V. Earley, R. I. Fryer, and R. Y. Ning, *J. Pharm. Sci.* **68**, 845 (1979).

<sup>167</sup> A. Silberg and Z. Frenkel, *Rev. Roum. Chim.* **10**, 1035 (1965).

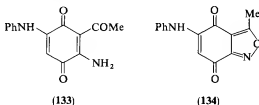
<sup>168</sup> A. I. Rachlin, U.S. Patent 3,261,870 (1966) [*CA* **65**, 15277 (1966)].

<sup>169</sup> M. S. Chauhan and D. M. McKinnon, *Can. J. Chem.* **53**, 1336 (1975).

<sup>170</sup> L. K. Dyal and J. E. Kemp, *Aust. J. Chem.* **20**, 1625 (1967); **26**, 1969 (1973).

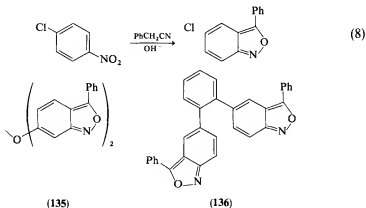
<sup>171</sup> L. K. Dyal, *Aust. J. Chem.* **32**, 643 (1979).

acetyldiamino-*p*-benzoquinone **133** with lead tetraacetate in chloroform furnishes the dioxoanthranil **134** in 72% yield.<sup>172</sup>



### 3. By Reaction of Benzyl Cyanides with Nitroarenes

The base-catalyzed reaction of benzyl cyanides with *p*-chloronitrobenzenes is widely used as a preparative route to 3-arylanthranils (Eq. 8), and hence, by reductive ring opening, *o*-aminobenzophenones, the valuable precursors of the pharmacologically important benzodiazepinones. By this method 3-phenylanthranils bearing trifluoromethoxy,<sup>173</sup> (trifluoromethyl)-thio,<sup>173</sup> sulfonamido,<sup>174</sup> methoxy- and ethoxycarbonyl,<sup>175,176</sup> cyano,<sup>175</sup> methylsulfonyl,<sup>175</sup> halo,<sup>176</sup> difluoromethoxy,<sup>177</sup> and acetyl (protected as the



<sup>172</sup> W. Schäfer, H. W. Moore, and A. Aguado, *Synthesis*, 30 (1974).

<sup>173</sup> F. J. McEvoy, E. N. Greenblatt, A. C. Osterberg, and G. R. Allen, *J. Med. Chem.* **11**, 1248 (1968).

<sup>174</sup> R. B. Moffett and A. D. Rudzik, *J. Med. Chem.* **14**, 588 (1971).

<sup>175</sup> M. Makosza and A. Zielinska, *Rocz. Chem.* **46**, 955 (1972).

<sup>176</sup> A. Jaszowska and B. Serafinowa, *Rocz. Chem.* **46**, 2051 (1972).

<sup>177</sup> S. A. Andronati, A. V. Bogatskii, G. N. Gordichik, Z. I. Zhilina, and L. M. Yagupolskii, *Khim. Geterotsikl. Soedin.*, 268 (1975).

ethylene ketal)<sup>178</sup> groups, as well as the bis(3-phenylanthranils) **135** and **136**<sup>179</sup> have been prepared, generally in 30–50% yield.

Occasionally, the reaction is complex and affords a multitude of products. For example, 2,4-dichloronitrobenzene and benzyl cyanide produce a mixture containing bis(4-chloro-2-benzoyl)azoxybenzene, 2-benzoyl-4-chloronitrobenzene, 5,7-dichloroanthranil, and  $\alpha$ -(5-chloro-2-nitrophenyl) benzyl cyanide.<sup>180</sup> Using sodium hydride in dimethylsulfoxide as the base, the substituted benzyl cyanide, formed by direct nucleophilic displacement of chloride, becomes the major product (48%), whereas with sodium hydroxide and benzyltriethylammonium chloride the dichloroanthranil (33%) predominates.

Nucleophilic displacement of halogen rather than anthranil formation is generally observed with *o*-nitrochlorobenzenes.<sup>1</sup> Of interest, therefore, is the formation of 5-benzoyl-7-chloro-3-phenylanthranil from 4-benzoyl-2-chloronitrobenzene and benzyl cyanide in the presence of potassium hydroxide.<sup>181</sup>

Attempts to prepare 3-(*p*-aminophenyl)-5-chloroanthranil from *p*-amino-benzyl cyanide and *p*-chloronitrobenzene failed. However, protection of the amino function as the dichloroacetyl derivative permits direct cyclization to the anthranil.<sup>182</sup>

2,5-Difluoronitrobenzene and ethyl cyanoacetate furnish 3-cyano-6-fluoroanthranil, albeit in poor yield (26%).<sup>183</sup> 2-Chloro-5-fluoronitrobenzene behaves similarly.

#### 4. From *o*-Azidocarbonyl Compounds

Thermal ring closures of *o*-azidoaldehydes and -ketones, like many other cyclizations involving azides adjacent to an  $\alpha,\beta$ -unsaturated function, involve a concerted process with concomitant loss of nitrogen rather than a nitrene reaction.<sup>184</sup> Kinetic studies demonstrate unequivocally that the carbonyl group exerts substantial anchimeric assistance. For example, the

<sup>178</sup> R. Y. Ning, P. B. Madan, and L. H. Sternbach, *J. Heterocycl. Chem.* **11**, 107 (1974); R. Y. Ning, Ger. Offen. 2,163,642 (1972) [77, 140181 (1972)]; U.S. Patent 3,900,501 (1975) [**84**, 44187 (1976)].

<sup>179</sup> S. O. Norris and J. K. Stille, *Macromolecules* **9**, 496 (1976); J. Garapon and J. K. Stille, *ibid.* **10**, 627 (1977).

<sup>180</sup> M. Makosza, J. M. Jagusztyn-Grochowska, and M. Jawdosiuk, *Rocz. Chem.* **50**, 1841 (1976).

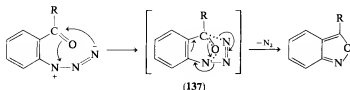
<sup>181</sup> M. Makosza and M. Ludwikow, *Rocz. Chem.* **51**, 829 (1977).

<sup>182</sup> C. Anghel, A. Mihon, and K. Lienert, *Stud. Univ. Babes-Bolyai, Ser. Chem.* **22**, 67 (1977) [*CA* **87**, 69 (1977)].

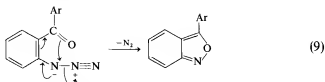
<sup>183</sup> A. Kalir and D. Balderman, *Isr. J. Chem.* **6**, 927 (1968).

<sup>184</sup> L. K. Dyal and J. E. Kemp, *J. Chem. Soc. B*, 976 (1968).

activation energies for decomposition of 2-acetyl and 2-benzoylphenyl azide are 25.8 and 27.2 kcal mol<sup>-1</sup>, respectively, compared with values of 32–40 kcal mol<sup>-1</sup> for unassisted aryl azide decompositions. However, the exact nature of this neighboring group effect is the subject of current debate. On the basis of a kinetic study on the rate of decomposition of 4'-substituted 2-azidobenzophenones to 3-arylanthranils, Hall and his co-workers<sup>185</sup> propose an intramolecular 1,3-dipolar cycloaddition process (137) to account for the enhanced rates of decomposition of these azides compared to phenyl azide.



This view has been challenged by Dyall,<sup>184</sup> who, also on the basis of kinetic data, favors an alternative 6 $\pi$ -pericyclic mechanism. (Eq. 9).

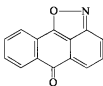


Dyall argues that the pericyclic process will be effective only if the participating  $\pi$ -orbitals all lie in the same plane. Hence, it should be more susceptible than the dipolar process to steric effects of groups adjacent to either the azide or carbonyl function. In addition, the already strained 1,3-dipolar adduct (137) should be sensitive to the steric requirement of group R. In fact, Dyall<sup>186</sup> has shown that for 2-azidoacetophenone a methyl group ortho to the azide or to the carbonyl function destroys virtually all rate-enhancement effects of the acetyl group. Also, he finds that 2-pivaloylphenyl azide, in which the bulky *t*-butyl group should hinder 1,3-dipolar cycloaddition of the azide to the carbonyl function, still displays a substantial rate enhancement (61.7-fold, relative to phenyl azide) on going to 3-*t*-butylanthranil. More dramatic is the  $2 \times 10^3$ -fold increase (relative to 1-azidonaphthalene) in the rate of decomposition of 1-azidoanthraquinone to the isoxazole 138. For this reaction, models show that an intermediate of type 137 is highly strained and would be expected to show only slight, if any, rate enhancement.

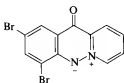
<sup>185</sup> J. H. Hall, F. E. Behr, and R. L. Reed, *J. Am. Chem. Soc.* **94**, 4952 (1972).

<sup>186</sup> L. K. Dyall, *Aust. J. Chem.* **30**, 2669 (1977).

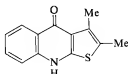
In practice, the azide decompositions are usually carried out in boiling toluene or xylene and give good yields of 3-alkyl-<sup>170,184,187</sup> and 3-aryl-anthranils.<sup>185,188</sup> Yields of 3-unsubstituted anthranils from *o*-azidobenzaldehydes are generally much lower.<sup>170</sup> The method has also been used to prepare 3-( $\beta$ -styryl)anthranils (**106**) from *o*-azidochalcones,<sup>189</sup> 3-methylnaphtho[2,3-*c*]isoxazoles from 3-acetyl-2-azidonaphthalene,<sup>190</sup> and 3-(2-pyridyl)anthranils from *o*-azidophenyl pyridyl ketones.<sup>191</sup> This last reaction is of interest in that 2-(2-azido-3,5-dibromobenzoyl)pyridine in boiling toluene yields almost equal amounts of 5,7-dibromo-3-(2-pyridyl)anthranil (43%) and the zwitterionic pyrido[1,2-*b*]cinnolin-6-ium **139** (41%).



(138)



(139)



(140)

Apparently, **139** is not formed by thermal rearrangement of the anthranil (see Section III.C.5.a) but directly from the azide, presumably by singlet nitrene attack at the pyridine ring nitrogen. Zwitterion **139** becomes the major product when the decomposition is carried out at higher temperature (215°C). Analogous by-products have also been noted in other azide decompositions. For example, low yields of 3-aryl-4-quinolones accompany 3-( $\beta$ -styryl)anthranil formation<sup>189</sup> (see also Section III.C.5.a).

Interestingly, preliminary studies indicate that some *o*-azidoaryl ketone  $\rightarrow$  anthranil decompositions are very sensitive to the presence of certain metals.<sup>132</sup> For example, although 2-(*o*-azidobenzoyl)-4,5-dimethylthiophene in boiling chlorobenzene yields 3-(4,5-dimethyl-3-thienyl)anthranil (94%), in the presence of reduced iron powder only thienoquinolone (**140**), i.e., the anthranil rearrangement product, is obtained in 67.5% yield. The nature and scope of this metal catalysis is currently under study.

*o*-Azidobenzoylazo compounds (**141**) undergo smooth thermal decomposition to 3-aryldiazoanthranils (**115**; R = N=NAr).<sup>192</sup>

<sup>187</sup> M. A. Ardakani and R. K. Smalley, *Tetrahedron Lett.*, 4769 (1979).

<sup>188</sup> A. O. Fitton and R. K. Smalley "Practical Heterocyclic Chemistry," p. 53. Academic Press, New York, 1968; D. H. Kenny and J. C. Strieter, *J. Chem. Educ.* **49**, 130 (1972).

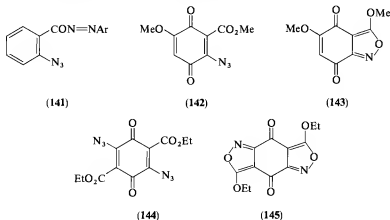
<sup>189</sup> R. K. Smalley, R. H. Smith, and H. Suschitzky, *Tetrahedron Lett.*, 2309 (1978).

<sup>190</sup> W. Friedrichsen and P. Kaschner, *Justus Liebigs Ann. Chem.*, 1959 (1977).

<sup>191</sup> R. Y. Ning, W. Y. Chen, and L. H. Sternbach, *J. Heterocycl. Chem.* **11**, 125 (1974).

<sup>192</sup> R. K. Smalley, R. H. Smith, and H. Suschitzky, *Tetrahedron Lett.*, 4687 (1979).

All attempts to generate 3-alkoxy- or 3-aryloxy-, 3-amino-, and 3-chloro-anthranils by thermolysis of *o*-azidoesters,<sup>169,170,184,193</sup> -amides,<sup>194</sup> and acid chlorides,<sup>194</sup> have so far failed. Dyall attributes (in part) the failure of *o*-azidoesters to yield 3-alkoxyanthranils to the enhanced resonance stabilization of the ester carbonyl relative to the ketone group.<sup>184</sup> However, in the *p*-benzoquinone series thermal azide cyclizations onto an adjacent ester grouping are well established; e.g., **142** → **143**.<sup>172,195</sup> In fact, the diazo-*p*-benzoquinone diester **144** decomposes in boiling benzene to give the benzo[1,2-*c*;4,5-*c'*]diisoxazole-4,8-dione **145** in 83% yield.<sup>196</sup>



In the absence of detailed mechanistic studies the reasons for this difference in thermal behavior of aryl and *p*-benzoquinone azides is not clear. However, the vinylic azide character of quinone azides may be an important factor.

Photodecomposition of *o*-azidoacetophenone appears to be exclusively via the singlet nitrene, and in nucleophilic solvents (methanol and piperidine) produces 3*H*-azepines (see Section III,C,7) rather than anthranils.<sup>197</sup> Surprisingly, however, and in contrast to other *o*-azidoamides which on photolysis in methanol yield 2-methoxy-3*H*-azepine-3-carboxyamides,<sup>198</sup>

<sup>193</sup> W. A. Strachan, Ph.D. Thesis, University of Salford, (1974).

<sup>194</sup> M. A. Ardakani and R. K. Smalley, *Tetrahedron Lett.*, 4765 (1979); also unpublished results.

<sup>195</sup> W. Schäfer, A. Aguado, and U. Sezer, *Angew. Chem., Int. Ed. Engl.* **10**, 406 (1971); W. Schäfer and H. Schlude, *Tetrahedron Lett.*, 4313 (1967).

<sup>196</sup> R. Neidlein, G. Humburg, A. Gieren, and C. Hahn, *Chem. Ber.* **111**, 3346 (1978).

<sup>197</sup> M. A. Berwick, *J. Am. Chem. Soc.* **93**, 5780 (1971).

<sup>198</sup> A. C. Mair and M. F. G. Stevens, *J. Chem. Soc. C*, 2317 (1971), R. Purvis, R. K. Smalley, W. A. Strachan, and H. Suschitzky, *J. C. S. Perkin. I*, 191 (1978).

photolysis of 2-azido-4-nitrobenzamide in methanol yields in addition to azo compound and the 2-amino-4-nitrobenzamide (typical triplet nitrene products), 3-amino-6-nitroanthranil as the major product (15%).<sup>199</sup> Triplet quenching experiments establish that the anthranil is formed via a singlet nitrene.

### 5. Miscellaneous

Anthranils have been isolated from the reduction of benzodiazepine di-*N*-oxides with hydrogen sulfide and from the dilute sodium hydroxide-induced ring contraction of benzodiazepinone *N*-oxides.<sup>200</sup>

Quantitative yields of 4,7-dioxoanthranils, e.g., **134**, are obtained on treating 3-acetyl-2,5-diarylamino-*p*-benzoquinones with hydroxylamine in boiling methanol.<sup>172,195,201</sup>

The production of anthranils by Beckmann rearrangement of the oximes of the photodimers of 2,6-dimethyl- $\gamma$ -pyrone, mentioned briefly in the original review, has been reported in detail.<sup>202</sup>

## B. PHYSICAL AND SPECTROSCOPIC PROPERTIES

Ground-state  $\pi$ -electronic charge densities calculated using semiempirical Pariser-Parr-Pople SCF-LCAO-MO methods predict electrophilic substitution of anthranil to occur at the 5- or 7-position.<sup>30,31,203</sup> In practice the 5-position is favored.<sup>1</sup> Also cited are the calculated energies of the highest occupied ( $-\epsilon_{\text{HO}}$  9.61) and lowest vacant ( $-\epsilon_{\text{LV}}$  2.15) molecular orbitals, and the total  $\pi$  energy ( $E_{\pi}$  - 334.74) of the ring system.<sup>30</sup>

Energy transitions and oscillator strengths for singlet and triplet states of anthranil, obtained by SCF-MO methods are in poor agreement with experimentally derived values.<sup>32</sup> However, later calculations of various ground-state properties such as <sup>1</sup>H- and <sup>13</sup>C-NMR shifts, ionization potentials, and dipole moments, using a modified CNDO-CI method agree well with experimental data.<sup>31</sup>

Solvent and substituent effects on the ultraviolet spectra of a series of 3-arylanthranils have been studied.<sup>204</sup> The He(I) photoelectron spectrum

<sup>199</sup> H. Nakayama, M. Nozawa, and Y. Kanaoka, *Chem. Pharm. Bull.* **27**, 2775 (1979).

<sup>200</sup> R. Y. Ning, R. I. Fryer, and B. C. Sluboski, *J. Org. Chem.* **42**, 3301 (1977).

<sup>201</sup> G. Kumar and A. P. Bhaduri, *Indian J. Chem.* **14B**, 575 (1976).

<sup>202</sup> P. Yates and E. S. Hand, *J. Am. Chem. Soc.* **91**, 4749 (1969).

<sup>203</sup> R. A. Sallavanti and D. D. Fitts, *Int. J. Quantum Chem.* **3**, 33 (1969).

<sup>204</sup> I. Hopartean, S. Mager, and M. Ionescu, *Stud. Univ. Babes-Bolyai, Ser. Chem.* **20**, 54 (1975) [*CA* **85**, 32147 (1976)].

and the high-resolution  $^1\text{H-NMR}$  spectra of anthranil and its 3-methyl derivative have been measured and are reproduced in Ref. 205 and 35, respectively. The chemical shift of the methyl group in *N*-methylantranilium perchlorate has been compared with the methyl chemical shifts of a series of other *N*-methylated azoles and their benzologs.<sup>36</sup>

## C. CHEMICAL PROPERTIES

### 1. Electrophilic Substitution

The nitration of 6-chloro- and 6-methoxyanthranils with potassium nitrate in concentrated sulfuric acid at  $-5^\circ\text{C}$  to give the 7-nitro derivatives appears to be the only example of electrophilic substitution of anthranils to be published in the period since the last review.<sup>206,207</sup>

### 2. Oxidation

Oxidation of 3-arylantranils is a useful preparative route to *o*-nitrobenzophenones, high yields being obtained with chromium trioxide in glacial acetic acid.<sup>176,180,181,208</sup> Per acids have also been used.<sup>168</sup> Failure to effect oxidation has been noted with potassium permanganate and with sodium dichromate in sulfuric acid.<sup>176</sup>

### 3. Reduction

The reduction of anthranils is a particularly valuable route to 5-chloro-2-aminobenzophenones, the precursors of benzodiazepinones of the Valium and Librium type. Reductions are successful with ferrous sulfate,<sup>209</sup> zinc,<sup>190</sup> or iron<sup>181</sup> in hydrochloric acid; iron in acetic acid<sup>154,155,175-177</sup>; zinc and calcium chloride in boiling ethanol<sup>165</sup>; and hydrazine hydrate in warm ethanol.<sup>154</sup> Phenylhydrazine reduces anthranils of type 134 to diamino-*p*-benzoquinones, e.g., 133.<sup>195</sup>

<sup>205</sup> M. H. Palmer and S. M. F. Kennedy, *J. Mol. Struct.* **43**, 33 (1978).

<sup>206</sup> A. J. Boulton and R. C. Brown, *J. Org. Chem.* **35**, 1662 (1970).

<sup>207</sup> S. N. Balasubrahmanyam, A. S. Radhakrishna, A. J. Boulton, and Thoe Kan-Woon, *J. Org. Chem.* **42**, 897 (1977).

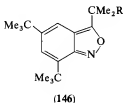
<sup>208</sup> A. Jaskowska and B. Serafin, *Rocz. Chem.* **48**, 1029 (1974).

<sup>209</sup> K. Reisinger and M. Pulster, Ger. Offen. 2,400,689 (1975) [*CA* **84**, 43633 (1976)].



Catalytic reductions using palladium charcoal,<sup>173,174,178,179,195</sup> platinum oxide,<sup>151,174</sup> or Raney nickel<sup>151</sup> and hydrogen are also common. 3-(5-Isothiazolyl)-5-chloroanthranil with palladium charcoal and hydrogen reduces to the chloroaminoketone without cleavage of the isothiazole ring.<sup>210</sup>

Despite this ease of hydrogenolysis, cases are known of both chemical and catalytic reductions in which substituents are reduced rather than the isoxazole ring. Examples include the nitroanthranil **128** ( $\text{Ar} = p\text{-MeOC}_6\text{H}_4$ ), which with zinc and acetic acid yields only the 4-aminoanthranil,<sup>151</sup> and surprisingly, the pyridylanthranil (**121**;  $\text{X} = \text{N}$ ,  $\text{H}$  in place of  $\text{NO}_2$ ) which with palladium charcoal and hydrogen in tetrahydrofuran at room temperature, is reduced to the 4,5,6,7-tetrahydroanthranil.<sup>148</sup> The cyanopropylanthranil **146** ( $\text{R} = \text{CN}$ ) with platinum oxide and hydrogen in ether solution is reduced to the amine (**146**;  $\text{R} = \text{CH}_2\text{NH}_2$ ), the anthranil ring remaining intact.<sup>159</sup>



Electrolytic reduction of 3-methylantranil in acid solution yields *o*-aminoacetophenone.<sup>211</sup>

#### 4. Reactions of Substituents

3-Methylantranil<sup>192</sup> and its 6-methoxy derivative<sup>135</sup> are readily brominated at the methyl group by *N*-bromosuccinimide. In contrast, 4-methoxy-3-methylantranil with one equivalent of *N*-bromosuccinimide yields only the 7-bromo derivative, whereas with an excess of reagent 7-bromo-3-(bromomethyl)-4-methoxyanthranil is obtained in 52% yield.<sup>135</sup>

The 3-(bromomethyl)anthranils have been used to prepare various 3-amino- and 3-alkylamino anthranils,<sup>135</sup> and by the Kröhnke method, anthranil-3-aldehyde in good overall yield.<sup>192</sup>

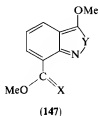
<sup>210</sup> R. Kalish, E. Broger, G. F. Field, T. Anton, T. V. Steppe, and L. H. Sternbach, *J. Heterocycl. Chem.* **12**, 49 (1975).

<sup>211</sup> H. Lund and A. D. Thomsen, *Acta Chem. Scand.* **23**, 3567 (1969).

Reduction of 3-benzoylanthranil to the secondary alcohol [**115**; R = CH(OH)Ph] proceeds smoothly with sodium borohydride, oxidation back to the ketone being achieved in hot nitrobenzene containing a small amount of *p*-toluenesulfonic acid.<sup>142</sup>

7-Hydroxy-3-methylantranil is methylated normally with methyl iodide and sodium carbonate to give the 7-methoxy derivative.<sup>135</sup> Anthranil carboxylic acids are converted into their acid chlorides by thionyl chloride,<sup>208</sup> and their methyl esters by diazomethane.<sup>169</sup> The acid chloride of 5-chloro-3-phenylantranil-6-carboxylic acid participates in the Friedel-Crafts acylation of benzene to give 6-benzoyl-5-chloro-3-phenylantranil (67%).<sup>208</sup>

Thionation of ester (**147**; X = Y = O) with phosphorus pentasulfide in toluene furnishes, in addition to the anticipated 2,1-benzisothiazole (**147**; X = Y = S), the thioester (**147**; X = S, Y = O) and the isomeric benzisothiazole (**147**; X = O, Y = S), this last product being formed by hydrolysis of the thioester during work-up.<sup>169</sup>



3-*p*-Tolylantranils condense with the anils of aromatic and heteroaromatic aldehydes in the presence of potassium hydroxide or *t*-butoxide in dimethylformamide to give 3-(stilben-4-yl)anthranils.<sup>74</sup>

3-(4-Pyrylium)anthranils, e.g., **121** (X = O<sup>+</sup>ClO<sub>4</sub><sup>-</sup>; H in place of NO<sub>2</sub>) with carbanions yield 3-arylantranils by a sequential ring-opening/ring-closure process.<sup>148</sup> For example, with nitromethane anthranil **115** (R = 3,5-Ph<sub>2</sub>-4-O<sub>2</sub>NC<sub>6</sub>H<sub>2</sub>) is obtained.

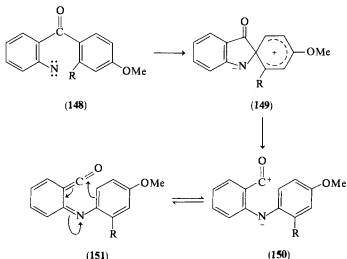
3-Alkoxyanthranil-4,7-diones, e.g., **143**, are susceptible to nucleophilic displacement of the alkoxy group and readily yield 3-alkylamino and 3-dialkylamino derivatives with primary and secondary amines, respectively.<sup>195</sup>

## 5. Ring Transformations

a. *To Acridones and Related Heterocycles.* The thermal and nitrous acid-induced conversion of 3-arylantranils to acridones is a well-established process.<sup>1,143</sup> However, Kwok and Pranc have shown that during the thermal

isomerization of 3-(2,4-dimethoxyphenyl)anthranil a hitherto unsuspected rearrangement occurs.<sup>212</sup> PMR spectroscopy demonstrates unequivocally that the product is the 2,4-dimethoxyacridone rather than the expected 1,3-dimethoxy derivative. Also, thermolysis of 3-(*p*-methoxyphenyl)-5-chloroanthranil yields a 3:1 mixture of 3-methoxy- and 2-methoxy-7-chloroacridone.

The authors explain their results in terms of initial ring opening of the anthranil to a nitrenoketone (148) followed by singlet, electrophilic nitrene attack at the electron-rich 1'-carbon position to yield the resonance-stabilized dipolar spiro intermediate 149. Acridone formation then occurs either via the polar intermediate 150 or, more likely, by electrocyclicization of its valence tautomer, the iminoketene 151.



Kwok and Pranc suggest that in the absence of a stabilizing (or activating) methoxyl group, nitrene attack will take place at the 2'-position to yield an unrearranged acridone. Preliminary results from our laboratories, however, indicate that spiro intermediates are involved in most if not all 3-arylanthranil  $\rightarrow$  acridone rearrangements.<sup>132</sup> For example (and contrary to earlier reports), thermal rearrangement of 3-(*p*-methylphenyl)anthranil produces a 1.43:1 mixture of 2- and 3-methylacridone, whereas 3-(2,4-dimethylphenyl)anthranil furnishes only rearranged product, i.e., 2,4-dimethylacridone (60%), along with the *o*-aminobenzophenone. Of particular interest is the thermal rearrangement of 3-mesitylanthranil which affords 2,4-dimethylacridone (46%), 2,4,10-trimethylacridone (4%), and, surprisingly,

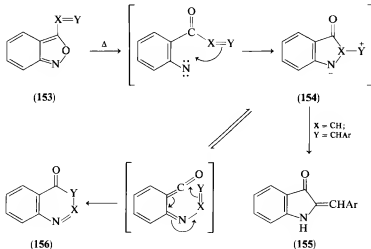
<sup>212</sup> R. Kwok and P. Pranc, *J. Org. Chem.* **33**, 2880 (1968).

2,4,5-trimethylacridone (16%). It is thought that this last product arises by two sequential [1,5]-sigmatropic shifts of the bridgehead methyl group in the initially formed trimethylacridone **152**.

Other exploratory studies on the rearrangement of 3-aryl- and 3-(thienyl)-anthranils to acridones and thienoquinolones, (e.g., **140**), respectively, indicate that these processes are catalyzed by transition metals (particularly iron powder), by various metal acetoacetate complexes, and by group 6 metal carbonyls. In fact, by a judicious choice of catalyst the anthranils can be made to yield either *o*-aminoketones or acridones as the major thermolysis products.<sup>132</sup>

6-Nitro-3-(2,5-dimethoxyphenyl)anthranil rearranges to 1,4-dimethoxyacridone, whereas the 6-nitro-3-(3,4-dimethoxyphenyl) derivative yields a mixture of rearranged and unrearranged dimethoxyacridones.<sup>165</sup>

Related are the thermal rearrangements undergone by 3- $\beta$ -styrylanthranils (**106**).<sup>187,189</sup> In boiling 1-methylnaphthalene (bp 245°C) the anthranils rearrange to 3-aryl-4-quinolones in practicable yields, whereas at 155–160°C (boiling anisole) 2-arylideneindoxyls (**155**) are formed. These results are rationalized in terms of the formation and subsequent rearrangement of, or proton loss from, the intermediate **154** (X = CH, Y = CHAr) (Scheme 17), which may be regarded as the acyclic equivalent of the spiro intermediate (**149**). 2-Aryl-4-quinolones, i.e., the products of a direct attack by the nitrene at the  $\beta$ -carbon center, are not formed.

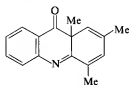


SCHEME 17

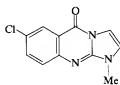
The scope of this reaction has been extended to include other anthranils bearing  $\alpha,\beta$ -unsaturated substituents at the 3-position. For example, anils

(**153**; X = CH, Y = NAr) rearrange to quinazolinones (**156**; X = CH, Y = NAr), and azoanthranils (**153**; X = N, Y = NAr) to 3-aryl-1,2,3-benzotriazin-4-ones (**156**; X = N, Y = NAr).<sup>192</sup> Reaction Scheme 17 also provides a rationale for the thermal rearrangement of 3-benzoylanthranil (**153**; X = CPh, Y = O) to 3-phenyl-3,1-benzoxazin-4-one (**156**; X = CPh, Y = O).<sup>213</sup>

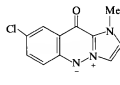
The products from the thermolysis of anthranils bearing a heteroaryl residue at position 3 are less predictable. 3-(2-Pyridyl)anthranils in boiling trichlorobenzene yield pyrido[1,2-*b*]cinnolin-6-iums (e.g., **139**) (cyclization of the initially formed nitrene taking place only at the electron-rich nitrogen center) and no rearranged products.<sup>191</sup> In contrast, the 3-(2-imidazolyl)-anthranil **108** (X = N, Y = CH) yields a mixture of the nitrene-induced rearrangement product (**157**) (63%) and the nitrene insertion product (**158**) (3%).<sup>131</sup> The 3-(5-pyrazolyl)anthranil **108** (X = CH, Y = N) behaves similarly.



(152)



(157)



(158)

A radical mechanism has been suggested to account for the thermal rearrangements of 3-phenyl-,<sup>143</sup> and 3-pentafluorophenyl-4,5,6,7-tetrafluoroanthranils,<sup>138</sup> to 1,2,3,4-tetrafluoro- and 1,2,3,4,5,6,7,8-octafluoro-acridones, respectively.

Evidence suggests that the nitrous acid-catalyzed rearrangement of 3-(*p*-methoxyphenyl)anthranils also proceeds via a spiro intermediate, although in some cases azoxy compounds are isolated rather than acridones.<sup>212</sup>

b. *To 2,1-Benzisothiazoles.* The conversion of anthranils into 2,1-benzisothiazoles is efficiently carried out by phosphorus pentasulfide in boiling toluene,<sup>169</sup> or by fusing the anthranil with phosphorus pentasulfide in the presence of imidazole.<sup>214</sup> 7-Acetyl-3-methylantranil with phosphorus pentasulfide in pyridine or carbon disulfide yields the corresponding benzisothiazole rather than the anthranilthio ketone.<sup>215</sup> It is suggested that this

<sup>213</sup> J. L. Pinkus, H. A. Jessup, and T. Cohen, *J. Chem. Soc. C*, 242 (1970).

<sup>214</sup> O. Aki, Y. Nakagawa, and K. Sirakawa, *Chem. Pharm. Bull.* **20**, 2372 (1972); Japanese Patent 73/08,098 [*CA* **79**, 78779 (1973)].

<sup>215</sup> D. M. McKinnon and J. Y. Wong, *Can. J. Chem.* **49**, 2018 (1971).

interconversion takes place by a rearrangement of the type described in the following section.

c. *Boulton-Katritzky-Type Rearrangements.* The thermal rearrangement of acylbenzofuroxans to nitroanthranils ( $159 \rightleftharpoons 160$ ) is well established.<sup>216</sup> An example of the reverse process is now apparent in the rearrangement of 6-chloro-7-nitroanthranil ( $160$ ;  $R^1 = \text{Cl}$ ,  $R^2 = \text{H}$ ) to 7-chlorobenzofuroxan-4-aldehyde ( $159$ ;  $R^1 = \text{Cl}$ ,  $R^2 = \text{H}$ ) in boiling acetic acid.<sup>206</sup> Steric inhibition of resonance of the nitro group in  $160$  with the aromatic ring is thought to be responsible for this anomalous behavior. More recent work shows that for the unsubstituted system ( $160$ ;  $R^1 = R^2 = \text{H}$ ) the two forms exist in equilibrium, the ratio of  $160:159$  being  $\sim 2$ .<sup>207</sup>



Variable-temperature  $^1\text{H-NMR}$  studies on 7-acetyl-3-methylantranil ( $161$ ;  $X = \text{O}$ ) indicate that there is a high interconversion energy barrier between the two identical valence tautomers.<sup>215</sup> In contrast, there is no evidence for a similar interconversion with the 7-acetylbenzothiazole ( $161$ ;  $X = \text{S}$ ),<sup>215</sup> nor for the methyl 3-methoxyanthranil-7-carboxylate ( $147$ ;  $X = Y = \text{O}$ ).<sup>169</sup>

7-Acetyl-3-methylantranil ( $161$ ;  $X = \text{O}$ ) with methylamine or aniline furnishes the 7-acetylpyrazoles ( $161$ ;  $X = \text{NMe}$  or  $\text{NPh}$ ) possibly by rearrangement of the initially formed iminoanthranils ( $161$ ;  $\text{NMe}$  or  $\text{NPh}$  in place of  $\text{O}$ ).<sup>215</sup>

3-Methyl-7-nitroanthranil ( $160$ ;  $R^1 = \text{H}$ ,  $R^2 = \text{Me}$ ) on treatment with triethyl phosphite rearranges to 4-acetylbenzofurazan, possibly by partial deoxygenation of the nitro group and then rearrangement of the resulting nitrosoanthranil.<sup>217</sup>

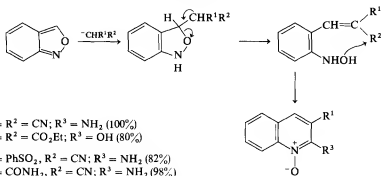
d. *To Quinolines.* Anthranil-3-acetic acid in boiling hydrochloric acid rearranges to 4-hydroxy-2-quinolone.<sup>146</sup> Quinoline *N*-oxides result by attack of carbanions at the 3-position of 3*H*-anthranils.<sup>218</sup> Representative examples

<sup>216</sup> A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.* **10**, 1 (1969).

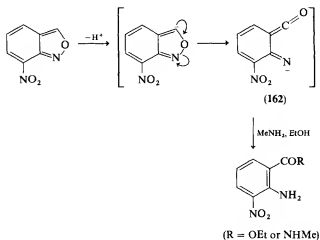
<sup>217</sup> A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *J. Chem. Soc. Chem. Commun.*, 62 (1968).

<sup>218</sup> E. C. Taylor and J. Bartulin, *Tetrahedron Lett.*, 2337 (1967).

(with yields) are appended to Scheme 18. The alternative and hitherto accepted behavior of 3-unsubstituted anthranils with base, i.e., abstraction of the 3-proton, rather than a Michael addition as proposed in Scheme 18, is discounted on the basis of deuterium labeling studies; anthranil, for example, with deuterium oxide and trimethylamine shows no exchange of the 3-proton even after 3 days. However, the authors' contention that all base-catalyzed ring cleavages of 3-unsubstituted anthranils proceed via the Michael addition route has been questioned by Boulton and his co-workers.<sup>207</sup> They find that the products from the reaction of 7-nitroanthranil with ethanolic methylamine are best explained by an initial proton abstraction from the 3-position followed by addition of ethanol or methylamine to the iminoketene (162) as outlined in Scheme 19.



SCHEME 18

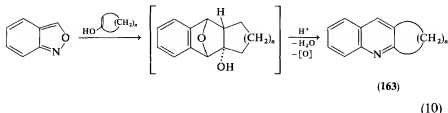


SCHEME 19

## 6. Cycloadditions

The cycloadducts from *N*-phenylmaleimide and anthranil have been reformulated.<sup>219</sup> The lower melting (mp 190°C) isomer is the *exo* rather than the *endo* adduct, whereas the supposed *exo* adduct (mp 231°C) is in fact (*o*-formylanilino)-*N*-phenylmaleimide. Cycloadducts have also been obtained with malcimine and its *N*-alkyl derivatives.<sup>220</sup>

The formation of acridine in the reaction of benzyne with anthranil is thought to be a stepwise rather than a concerted (4 + 2)-cycloaddition.<sup>221</sup> More interesting are the mercury sulfate-catalyzed cycloadditions of alicyclic ketones to anthranil in boiling xylene, which appear to involve the enol tautomers as indicated in Eq. (10).<sup>222</sup> The yields of 2,3-cycloalkanoquinolines (**163**) range from 11% (*n* = 4) to 39% (*n* = 5). Phenylacetylene and diethyl maleate yield similar products.



## 7. Photolysis

The photolytic behavior of anthranils is highly dependent on the pH of the reaction medium. In neutral or basic solution anthranils lacking a 7-substituent cleave to give *o*-nitrenoacyl compounds which, in the presence of a suitable nucleophile (alcohols, amines, or water), undergo ring expansion to 3*H*-azepines (or azepinones) by the route shown in Scheme 20.<sup>197,223,224</sup> However, if the 7-position is blocked by an aryl group, then an alternative photorearrangement to acridones takes place, probably via a spiro intermediate of type **149**.<sup>223</sup>

Photolysis of 3-(pentafluorophenyl)anthranil in light petrol yields 2'-amino-2,3,4,5,6-pentafluorodiphenyl ketone.<sup>143</sup>

<sup>219</sup> E. C. Taylor, D. R. Eckroth, and J. Bartulin, *J. Org. Chem.* **32**, 1899 (1967).

<sup>220</sup> V. P. Arya and S. J. Shenoy, *Indian J. Chem.* **14B**, 780 (1976).

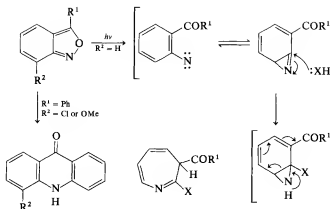
<sup>221</sup> C. D. Campbell and C. W. Rees, *J. Chem. Soc., C*, 748 (1969).

<sup>222</sup> M. Wilk, H. Schwab, and J. Rochlitz, *Justus Liebigs Ann. Chem.* **698**, 149 (1966).

<sup>223</sup> M. Ogata, H. Matsumoto, and H. Kano, *Tetrahedron* **25**, 5205 (1969).

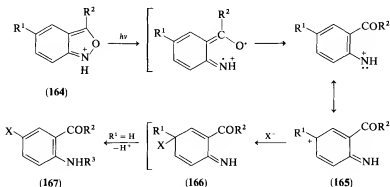
<sup>224</sup> W. Heinzelmänn and M. Märky, *Helv. Chim. Acta* **56**, 1852 (1973).





SCHEME 20

The photochemical behavior of anthranils in acid solution is more complex. In general, mixtures of 3- and 5-substituted 2-aminoacylbenzenes are formed by conjugate addition of the acid to the initially formed resonance-stabilized nitrenium ion as outlined in Scheme 21 for 5-substitution (generally the major product).<sup>225,226</sup>



SCHEME 21

If the 5-position is blocked, e.g., **164** ( $\text{R}^1 = \text{R}^2 = \text{Me}$ ), then photolysis in sulfuric acid followed by acetylation of the photolysate yields a mixture of aminoketone (**167**;  $\text{X} = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{Ac}$ ), the acetoxymethyl derivative

<sup>225</sup> E. Giovannini, J. Rosales, and B. F. S. E. de Sousa, *Helv. Chim. Acta* **54**, 2111 (1971).

<sup>226</sup> M. Georgarakis, T. Doppler, M. Märky, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **54**, 2916 (1971).

(167;  $X = \text{CH}_2\text{OAc}$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{Ac}$ ) and 3-acetoxy-6-acetamido-2-methylacetophenone, this last product being formed by a methyl migration in the intermediate 166 ( $R^1 = R^2 = \text{Me}$ ,  $X = \text{OSO}_2\text{OH}$ ).<sup>227</sup>

Photolysis of 3,5-diphenylanthranil in concentrated hydrochloric acid produces 5-(*p*-chlorophenyl)-2-aminobenzophenone as expected from a consideration of mesomeric structures (165;  $R^1 = \text{Ph}$ ).<sup>228</sup> 5-Halogeno-3-phenylanthranils under similar conditions yield 3,5-dihalogeno-2-aminobenzophenones, whereas photolysis in concentrated sulfuric acid results in substitution (by hydroxy) and migration of the halogen to give 2-amino-6-halogeno-5-hydroxybenzophenones in 25–35% yield. Irradiation of 3-phenylanthranils in hydrobromic acid is somewhat different in that unsubstituted *o*-aminobenzophenones are produced in addition to their bromo derivatives.<sup>228</sup>

The role of singlet and triplet nitrenium ions in these reactions has been evaluated.<sup>228,229</sup> Convincing evidence for the participation of singlet ground-state 2-acetylphenyl nitrenium ions during the photodecomposition of 3-methylanthranils in concentrated sulfuric acid has been obtained.<sup>229</sup> For example, in the presence of arenes or anisole, in addition to the usual products, substantial amounts of diphenylamines and 3- and 5-(*p*-methoxyphenyl)-2-aminoacetophenones, respectively, are formed by electrophilic attack of the nitrenium ion on the added substrate.

### 8. Miscellaneous Reactions

A novel one-step synthesis of tricycloquinazolines has been described which involves treating anthranils with ammonium acetate in a mixture of acetic acid and sulfolane.<sup>230</sup> Anthranils and triphenylphosphine in boiling toluene provide a useful synthesis of *o*-acyliminophosphoranes (168).<sup>231</sup>



3-Arylanthranils with thionyl chloride at room temperature, followed by trituration with methanol, ring-open to 3-chloro-2-aminobenzophenones as

<sup>227</sup> T. Doppler, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta* **55**, 1730 (1972).

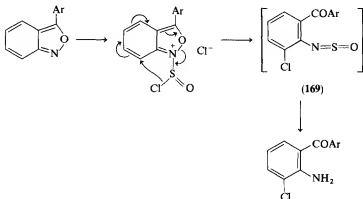
<sup>228</sup> E. Giovannini and B. F. S. E. de Sousa, *Helv. Chim. Acta* **62**, 185, 198 (1979).

<sup>229</sup> T. Doppler, H. Schmid, and H.-J. Hansen, *Helv. Chim. Acta* **62**, 271, 304 (1979).

<sup>230</sup> F. Yoneda and K. Mera, *Chem. Pharm. Bull.* **21**, 1610 (1973).

<sup>231</sup> Y. Nomura, Y. Kikuchi, and Y. Takeuchi, *Chem. Lett.*, 575 (1974).

shown in Scheme 22. All attempts to isolate the sulfinylamine (**169**) have so far failed.<sup>232</sup>



SCHEME 22

#### D. ANTHRANILUM SALTS

*N*-Alkylation of anthranils has been achieved using *t*-butyl alcohol in 60% perchloric acid,<sup>233,234</sup> methyl fluorosulfonate,<sup>235</sup> dimethyl sulfate,<sup>236</sup> triethyloxonium tetrafluoroborate,<sup>237</sup> and, unusually, trialkyl orthoformates in the presence of boron trifluoride etherate.<sup>237</sup> Rate studies for the *N*-methylation of anthranils in dimethyl sulfate are available.<sup>36</sup>

*N*-Alkylanthranilium salts, like their parent anthranils, are readily reduced to 2-alkylaminoacylbenzenes. Sodium dithionite,<sup>236,237</sup> zinc,<sup>237</sup> or iron in acetic acid,<sup>238</sup> and palladium charcoal and hydrogen<sup>238,239</sup> are the usual reducing agents. Reduction with sodium borohydride produces the synthetically useful benzisoxazolines (**170**) in high yield<sup>233,237</sup> (see Section III,G,1).

<sup>232</sup> R. C. Boruah, J. S. Sandhu, and G. Thyagarajan, *J. Heterocycl. Chem.* **16**, 1087 (1979).

<sup>233</sup> R. V. Coombs and G. E. Hardtmann, *J. Org. Chem.* **35**, 2440 (1970); R. V. Coombs, G. E. Hardtmann, and E. Goetz, U.S. Patent 3,911,132 (1975) [*CA* **84**, 31040 (1976)]; U.S. Patent 3,541,151 (1970) [*CA* **74**, 125720 (1971)]; U.S. Patent 3,931,172 (1976) [*CA* **84**, 90141 (1976)].

<sup>234</sup> R. A. Olofson, R. K. VanderMeer, and S. Stourmas, *J. Am. Chem. Soc.* **93**, 1543 (1971).

<sup>235</sup> N. F. Haley, *J. Org. Chem.* **43**, 1233 (1978).

<sup>236</sup> A. Novacek, Czech Patent 164,184 (1976) [*CA* **86**, 106178 (1977)].

<sup>237</sup> Y. Nakagawa, O. Aki, and K. Sirakawa, *Chem. Pharm. Bull.* **20**, 2209 (1972).

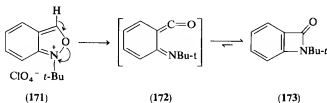
<sup>238</sup> K. W. Gopinath, J. S. Sandhu, D. S. Mago, and A. Kumar, British Patent 1,460,141 (1976) [*CA* **87**, 22781 (1977)]; Japan Kokai 77/51,350 [*CA* **88**, 37423 (1978)].

<sup>239</sup> H. von Brachel, H. Bender, and H. Kindler, Ger. Offen. 1,902,412 (1970) [*CA* **73**, 76882 (1970)].



(170)

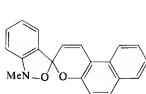
These salts are exceptionally reactive toward nucleophilic attack at the 3-position and a variety of stable adducts [(170);  $R^1 = \text{H}$ , alkyl, or aryl,  $R^2 = \text{alkyl}$ ,  $R^3 = \text{CN}$ , alkyl,  $\text{CH}(\text{CO}_2\text{Et})$ ,  $\text{NR}_2$ , and  $\text{OMe}$ ] have been prepared.<sup>234,235,237</sup> The adducts [(170);  $R^1 = \text{Et}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{NCO}$  or  $\text{N}_3$ ] are unstable and rearrange, via the acyl isocyanate and the acyl azide, respectively, to *N*-ethylbenzimidazolone and 1-ethylquinazoline-2,4-dione<sup>234</sup> (see also Section III,G,1). Of particular interest is the action of triethylamine on the *t*-butyl derivative (171). Initial loss of the 3-proton is followed by ring opening to the iminoketene (172) which undergoes electrocyclicization to its stable valence tautomer the *N*-*t*-butylbenzazetidone (173) in 84% yield.<sup>234</sup>



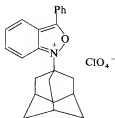
3-Methylantranilium salts condense readily with aldehydes, ketones, orthoesters, and diazonium salts to yield styryl, cyanine, and azo dyes, respectively.<sup>235</sup> An interesting aspect of these anthranilium salts is their bifunctionality, the 3-methyl group being nucleophilic whereas the C-3 position is electrophilic. As a consequence, base-catalyzed condensation with aldehydes bearing a nucleophilic function at the ortho position (e.g., 2-hydroxy-1-naphthaldehyde) allow thermochromic spiroisoxazolines, e.g., 174, to be prepared.<sup>235</sup>

In view of the results discussed in Section III,C,7, it is not surprising that photolysis of *N*-alkylantranilium perchlorates in aqueous solution leads to the formation of 3- and 5-hydroxy-2-alkylaminoacylbenzenes.<sup>240</sup> Addition of inorganic ions (e.g.,  $\text{Cl}^-$ ,  $\text{Br}^-$ , or  $\text{SCN}^-$ ) produces the correspondingly 3- and 5-substituted 2-aminoketones. However, a unique reaction occurs with the *N*-adamantyl perchlorate 175, which in acetonitrile suffers expansion of the adamantyl ring to give what is thought to be a 3-azahomoadamantene.<sup>240</sup>

<sup>240</sup> N. F. Haley, *J. Org. Chem.* **42**, 3929 (1977).



(174)



(175)

### E. ANTHRANIL *N*-OXIDES

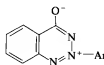
The long-standing problem<sup>1</sup> concerning the structure of the products obtained by oxidation of *o*-nitrobenzaldehyde arylhydrazones with either bromine or lead tetraacetate has been settled. Kerber, mainly on the basis of spectroscopic evidence and mechanistic reasoning, rejected the 3-arylaazoanthranil *N*-oxide structure (176) in favor of a 2-aryl-1,2,3-benzotriazin-4-ylidene *N*-oxide (177).<sup>2,41</sup> The structures of the deoxygenated derivatives (178) of 177 have since been confirmed by unambiguous synthesis.<sup>2,42</sup>



(176)



(177)



(178)

In view of these results it must be concluded that the other "anthranil *N*-oxides" obtained by oxidation of *o*-nitrobenzaldehyde phenylhydrazones,<sup>2,43</sup> or by solvolysis of their  $\alpha$ -bromo derivatives,<sup>2,44</sup> should be reformulated as benzotriazin-4-ylidene *N*-oxides. However, it is quite likely that 3-arylaazoanthranil *N*-oxides are intermediates in these reactions and also in the photolytic rearrangement of  $\alpha$ -bromo-*o*-nitrobenzaldehyde phenylhydrazones to 3-aryl-1,2,3-benzotriazin-4-ones.<sup>2,45</sup>

3-Pentafluorophenylanthranil *N*-oxide has been reported from the reaction of 2,3,4,5,6-pentafluoro-2'-nitrodiphenylmethanol with concentrated sulfuric acid.<sup>1,43</sup> However, in view of the doubts associated with the structures

<sup>2,41</sup> R. C. Kerber, *J. Org. Chem.* **37**, 1587 (1972).

<sup>2,42</sup> A. McKillop and R. J. Kobylecki, *J. Org. Chem.* **39**, 2710 (1974).

<sup>2,43</sup> W. A. F. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc. C*, 2587 (1969).

<sup>2,44</sup> A. F. Hegarty, M. Cashman, J. B. Aylward, and F. L. Scott, *J. Chem. Soc. B*, 1879 (1971);

J. B. Aylward, *Malays. J. Sci.* **1**, 145 (1972) [*CA* **79**, 77645 (1973)].

<sup>2,45</sup> Y. Maki and T. Furuta, *Synthesis*, 382 (1978).

of products from similar acid-induced cyclizations,<sup>1</sup> the validity of this *N*-oxide structure must await further confirmation. Equally, the claim that the anthranil-3,7-dione *N*-oxide **179** is formed in the cyclodehydration of 3-hydroxy-4-methyl-2-nitrobenzoic acid with dicyclohexylcarbodiimide<sup>246</sup> requires verification.

In light of the arguments put forward in the original review against the anthranil *N*-oxide structures,<sup>1</sup> it is pertinent to mention that infrared and proton magnetic resonance spectroscopic data on *o*-nitrosobenzaldehyde indicate that it exists entirely as the nitrosoaldehyde and not in equilibrium with the isomeric anthranil *N*-oxide.<sup>247</sup>

## F. 2,1-BENZISOXAZOLIN-3-ONES

The most convenient method for preparing 2,1-benzisoxazolin-3-ones is by zinc-ammonium acetate (or chloride) reduction of *o*-nitrobenzoates.<sup>248,249</sup> The resulting *o*-hydroxyaminoesters undergo rapid acid- or base-catalyzed intramolecular displacement of alcohol with concomitant formation of the benzisoxazolin-3-one.

*o*-Hydroxyaminoesters (**180**;  $R^1 = \text{OEt}$ ,  $R^2 = \text{H}$ ) and isocyanates ( $R^3\text{NCO}$ ) yield *N*-hydroxyureas (**180**;  $R^1 = \text{OEt}$ ,  $R^2 = \text{CONHR}^3$ ) which in triethylamine-pyridine cyclize to 1-ureidobenzisoxazolin-3-ones (**181**;  $R^1 = \text{CONHR}^3$ ,  $R^2 = \text{H}$ ).<sup>250</sup> Cyclization of the *N*-methylurea **180** ( $R^1 = \text{OEt}$ ,  $R^2 = \text{CONHMe}$ ) is also effected by diphenyldiazomethane.<sup>251</sup> Cyclic carbamates (**181**;  $R^1 = \text{CO}_2\text{R}$ ,  $R^2 = \text{H}$ ) are formed by treating acid **180** ( $R^1 = \text{OH}$ ,  $R^2 = \text{H}$ ) with chloroformates in diethyl ether.<sup>252</sup>



(179)



(180)



(181)

<sup>246</sup> E. N. Glibin, B. V. Tsukerman, S. S. Tsybalova, and O. F. Ginzburg, *J. Org. Chem. USSR (Engl. Transl.)* **13**, 421 (1977).

<sup>247</sup> J. M. Bakke and H.-J. Egan, *Acta Chem. Scand.* **32B**, 230 (1978).

<sup>248</sup> D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J. C.S. Perkin I*, 599 (1973).

<sup>249</sup> B. G. Cox, D. McL. A. Grieve, and A. E. A. Porter, *J. C.S. Perkin II*, 1512 (1975); B. G. Cox, R. J. Gillespie, R. S. Hay, A. E. A. Porter, and J. S. Roberts, *ibid.*, 904 (1977).

<sup>250</sup> R. Stoffel and H.-J. Bresse, *Arch. Pharm. (Weinheim, Ger.)* **306**, 579 (1973).

<sup>251</sup> L. Capuano and W. Ebner, *Chem. Ber.* **102**, 1480 (1969).

<sup>252</sup> G. S. Shvindlerman, Yu. A. Baskakov, and T. V. Gorskaya, USSR Patent 246,518 (1969) [*CA* **71**, 101844 (1969)]; G. S. Shvindlerman, Yu. A. Baskakov, and Z. I. Karachunskaya, USSR Patent 247,308 (1969) [*CA* **72**, 3478 (1970)]; USSR Patent 266,772 (1970) [*CA* **73**, 25434 (1970)].

Electrolytic reduction of *o*-nitrobenzohydrazide affords mainly 1,2,3-benzotriazin-4-one together with trace amounts of 2,1-benzisoxazolin-3-one.<sup>253</sup> All three isomeric naphthoisoxazolin-3-ones may be prepared in reasonable yield by electrolytic reduction of the appropriate nitroamide in ethanolic ammonium acetate.<sup>254</sup>

2,1-Benzisoxazolin-3-one is an intermediate in the reduction of *o*-nitro-*N,N*-dimethylbenzamide by sodium borohydride in the presence of palladium charcoal, and has been trapped as its *N*-acetyl derivative.<sup>255</sup> *N*-Benzoyl-5-chloro-2,1-benzisoxazolin-3-one (**181**;  $R^1 = \text{Bz}$ ,  $R^2 = \text{Cl}$ ), obtained from the oxidation of 6-chloro-1,3-dihydroxy-2-phenyl-4-quinolone with potassium permanganate in cold acetic acid, arises most probably by cyclodehydration of the *N*-acylhydroxamic acid (**180**;  $R^1 = \text{OH}$ ,  $R^2 = \text{Bz}$ ).<sup>256</sup>

Surprisingly, 3-cyano-1-hydroxy-2-methylindole with potassium permanganate or sodium dichromate suffers only dehydroxylation, whereas with 35% nitric acid in benzene a 68% yield of *N*-acetyl-2,1-benzisoxazolin-3-one (**181**;  $R^1 = \text{Ac}$ ,  $R^2 = \text{H}$ ) is obtained. Oxidation with 70% nitric acid produces the nitro derivative **181** ( $R^1 = \text{Ac}$ ,  $R^2 = \text{NO}_2$ ) in high yield (70%).<sup>257</sup> The *N*-acetylacetyl cyanide **180** ( $R^1 = \text{CN}$ ,  $R^2 = \text{Ac}$ ) is the presumed intermediate.

## G. REDUCED DERIVATIVES

### 1. Dihydroanthranils

*N*-*t*-Butylbenzisoxazolines (**170**;  $R^1 = t\text{-Bu}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{Ar}$ ), prepared by sodium borohydride reduction of the anthranilium salts (see Section III.D), on heating at 150–160°C isomerize to *o*-*t*-butylaminoacylbenzenes.<sup>253</sup> The reaction has merit as a preparative route to *o*-aminobenzaldehydes, especially as only neutral conditions are employed.

*N*-*t*-Butylbenzisoxazolin-3-ol (**170**;  $R^1 = t\text{-Bu}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{OH}$ ) is thermally unstable and in boiling benzene affords *o*-*t*-butylaminobenzoic anhydride. Oxidation with dicyanodichloro-*p*-benzoquinone yields *N*-*t*-butylbenzoxazolin-3-one.<sup>258</sup>

<sup>253</sup> R. Hazard and A. Tallec, *Bull. Soc. Chim. Fr.*, 433 (1976).

<sup>254</sup> M. Jubault and D. Peltier, *Bull. Soc. Chim. Fr.*, 1561 (1972); M. Jubault, *C. R. Acad. Sci., Ser. C* **270**, 1671 (1970).

<sup>255</sup> T. Cohen and W. F. Gray, *J. Org. Chem.* **37**, 741 (1972).

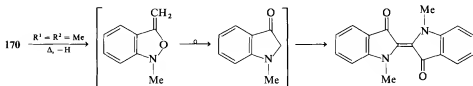
<sup>256</sup> I. P. Sword, *J. Chem. Soc. C*, 820 (1971).

<sup>257</sup> I. P. Sword, *Chem. Ind. (London)*, 166 (1972).

<sup>258</sup> R. V. Coombs, *J. Org. Chem.* **42**, 1812 (1977).

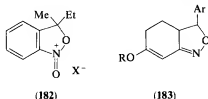
The structure of Bamberger's "agnetobenzaldehyde," an intermediate in the acid-catalyzed rearrangement of *o*-nitrobenzyl alcohol to *o*-nitrosobenzaldehyde, has been formulated as the 2,1-benzisoxazolin-3-ol [**170**;  $R^1 = o\text{-NO}_2\text{C}_6\text{H}_4\text{CH(OH)}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{OH}$ ]. Acetic anhydride converts it into the *N*-acetyl derivative (**170**;  $R^1 = \text{Ac}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{OH}$ ) which with calcium hypochlorite is oxidized to *o*-nitrosobenzaldehyde.<sup>247</sup>

Benzisoxazolines (**170**;  $R^1 = \text{Et}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{CN}$ ,  $\text{N}_3$ , or  $\text{OMe}$ ) are reported to undergo thermal ring opening and rearrangement to a variety of heterocycles.<sup>234</sup> However, the analogous 1,3-dimethyl derivatives (**170**;  $R^1 = R^2 = \text{Me}$ ,  $R^3$  as before) behave quite differently in that at  $130^\circ\text{C}$  they eliminate  $\text{HR}^3$  to yield *N,N'*-dimethylindigo by the sequence outlined in Scheme 23.<sup>235</sup>



SCHEME 23

Silver ions catalyze the isomerization of *o*-nitrocyclopropylbenzenes and *o*-nitrostyrenes to **182** ( $\text{X} = \text{BF}_4$  or  $\text{SbF}_6$ ).<sup>259</sup> The corresponding hydro-sulfates (**182**;  $\text{X} = \text{HSO}_4$ ) are moderately stable intermediates in the rearrangement of *o*-nitrocyclopropylbenzenes to *o*-nitrosoketones in concentrated sulfuric acid. These unusual structures are characterized by two intense absorption bands in the infrared spectra at 1570–1575 and 1650–1655  $\text{cm}^{-1}$ .  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data for (**182**) are also cited.



4,5-Dihydro-6-alkoxy-3-aryl (or heteroaryl)-anthranils, e.g., **183**, prepared by the action of hydroxylamine hydrochloride in pyridine on 3-alkoxy-6-acylcyclohex-2-en-1-ones, show antitubercular activity.<sup>260</sup>

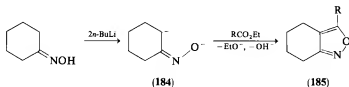
<sup>259</sup> Yu. S. Shabarov, S. S. Mochalov, and V. I. Daineko, *J. Org. Chem. USSR (Engl. Transl.)* **12**, 1293 (1976); **10**, 2331 (1974); V. I. Daineko, V. A. Chertkov, S. S. Mochalov, and Yu. S. Shabarov, *ibid.*, 2536.

<sup>260</sup> N. Sugimoto, H. Kugita, M. Tanaka, and H. Inoue, Japanese Patent 66/16,167 [*CA* **66**, 10924 (1967)]; Japanese Patent 66/16,168 [*CA* **66**, 10925 (1967)].



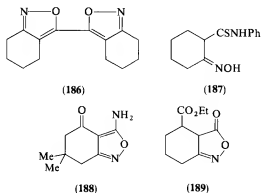
## 2. Tetrahydroanthranils

As discussed in Section II,D,2, the action of hydroxylamine on *o*-acylcyclohexanones generally produces an inseparable mixture of 4,5,6,7-tetrahydro-1,2- and -2,1-benzisoxazoles, the latter, except in a few instances, being the major products.<sup>92-94,261</sup> Synthesis of 4,5,6,7-tetrahydroanthranils free from contamination by indoxazenes is now possible by condensing esters with 1,4-dianions, e.g., **184**, derived from oximes having an  $\alpha$ -hydrogen, as exemplified in Scheme 24.<sup>262</sup>



SCHEME 24

Diethyl oxalate and dianion **184** yield the bistetrahydroanthranil **186** in 59% yield.<sup>263</sup> The yields of tetrahydroanthranils are improved by using *N,N*-dimethylamides in place of esters.<sup>264</sup> For example, with dimethylformamide, dianion **184** affords 4,5,6,7-tetrahydroanthranil in 81% yield, compared with only 22% using ethyl formate.



<sup>261</sup> W. L. Meyer, R. W. Huffman, and P. G. Schroeder, *Tetrahedron* **24**, 5959 (1968).

<sup>262</sup> C. F. Beam, M. C. D. Dyer, R. A. Schwarz, and C. R. Häuser, *J. Org. Chem.* **35**, 1806 (1970); C. F. Beam, K. D. Shealy, C. E. Harris, N. L. Shealy, L. W. Dasher, W. M. Hollinger, R. M. Sandifer, and D. C. Reames, *J. Pharm. Sci.* **65**, 1408 (1976).

<sup>263</sup> R. M. Sandifer, L. W. Dasher, W. M. Hollinger, C. W. Thomas, D. C. Reames, C. F. Beam, R. S. Foote, and C. R. Häuser, *J. Heterocycl. Chem.* **12**, 1159 (1975).

<sup>264</sup> G. N. Barber and R. A. Olofson, *J. Org. Chem.* **43**, 3015 (1978).

The nitrosyl chloride adduct of cyclohexene (as the  $\alpha$ -chlorooxime) condenses with sodium or potassium cyanide in dimethyl sulfoxide (or ethanol) to yield 3-amino-4,5,6,7-tetrahydroanthranil (**185**;  $R = NH_2$ ).<sup>265,266</sup> Cyclization of the oximinothioamide **187** with alkoxide proceeds via loss of  $SH^-$  to give the 3-anilino-tetrahydroanthranil (**185**;  $R = PhNH$ ). In methanolic hydrogen chloride, however, aniline is eliminated and the unstable 4,5,6,7-tetrahydroanthranil-3-thiol (**185**;  $R = SH$ ) is produced in 30% yield.<sup>267</sup>

A mixture of 3-amino-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroanthranil (**188**) and the isomeric tetrahydroindoxazene is formed on treating 2-cyano-5,5-dimethyl-3-ethoxycyclohex-2-en-1-one with hydroxylamine.<sup>268</sup>

Attempts to aromatize 4,5,6,7-tetrahydroanthranils have met with only moderate success.<sup>2</sup> The 3-cyclohexyl derivative is unaffected by sulfur at 200°C and by chloranil, whereas the 3-methyl and 3-phenyl derivatives with 5% palladium charcoal in boiling decalin yield only *o*-aminoacylketones. However, dibromination (probably at positions 4 and 7) of **185** ( $R = Ph$ ) with *N*-bromosuccinimide followed by dehydrobromination in methanolic potassium hydroxide furnishes 3-phenylanthranil.

Reduction of the *o*-nitrobenzoyl derivative of **185** ( $R = NH_2$ ) with Raney nickel and hydrogen brings about ring transformation to 5,6,7,8-tetrahydro-2-(*o*-aminophenyl)pyrimidin-4-one.<sup>269</sup>

### 3. Hexahydroanthranils

3,3a,4,5,6,7-Hexahydro-3-oxo-2,1-benzisoxazoline carboxylates (e.g., **189**), prepared by the acid-catalyzed cyclization of cyclohexanone mono- and dicarboxylate oximes, are reduced by Raney nickel and hydrogen to 4-amino-cyclohexane-1-carboxylates.<sup>270</sup>

A novel and potentially useful preparation of hexahydroanthranils is by intramolecular 1,3-dipolar cycloadditions of  $\epsilon,\zeta$ -unsaturated nitrile oxides.<sup>271</sup> Yields are almost quantitative.

<sup>265</sup> M. Ohno and N. Naruse, *Bull. Chem. Soc. Jpn.* **39**, 1125 (1966); M. Ohno, N. Kawabe, and M. Okamoto, Japanese Patent 73/04,781 [*CA* **78**, 147939 (1973)].

<sup>266</sup> M. Dines and M. L. Scheinbaum, *Tetrahedron Lett.*, 4817 (1969).

<sup>267</sup> G. Griss and H. Machleidt, *Justus Liebigs Ann. Chem.* **738**, 60 (1970).

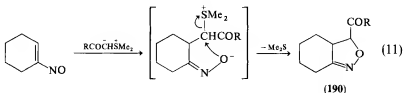
<sup>268</sup> A. Ya. Strakov, M. B. Andaburskaya, A. M. Moiseenkov, and A. A. Akhrem, *Latv. P.S.R. Zinat Akad. Vestis, Kim. Ser.*, 330 (1973) [*CA* **79**, 92147 (1973)].

<sup>269</sup> S. Pleschia, E. Ajello, V. Sprio, and M. L. Marino, *J. Heterocycl. Chem.* **11**, 603 (1974).

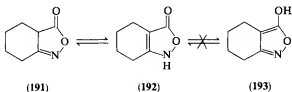
<sup>270</sup> V. Škarić, B. Djuras, and V. Turjak-Zebić, *Croat. Chem. Acta* **48**, 341 (1976) [*CA* **86**, 71983 (1977)]; J. C. S. Perkin I, 1959 (1975), V. Škarić, B. Djuras, and D. Škarić, *Croat. Chem. Acta* **47**, 145 (1975) [*CA* **84**, 43401 (1976)].

<sup>271</sup> V. Jäger and H. J. Günther, *Angew. Chem., Int. Ed. Engl.* **16**, 246 (1977).

1-Nitrosocyclohexene, derived by dehydrochlorination of  $\alpha$ -chlorocyclohexanone oxime, suffers nucleophilic attack by acylsulfonium ylides to give ultimately 3-acyl-3,3a,4,5,6,7-hexahydroanthranils (**190**) in practicable yields (Eq. 11).<sup>272</sup>

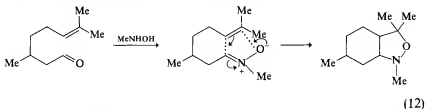


Hexahydro-2,1-benzisoxazolin-3-ones exist as mixtures of tautomers (**191**  $\rightleftharpoons$  **192**).<sup>273</sup> Infrared, ultraviolet, and <sup>1</sup>H-NMR spectroscopy fails to detect the hydroxy tautomer (**193**).



#### 4. Octahydroanthranils

Octahydroanthranils result from the intramolecular 1,3-dipolar cycloaddition of  $\epsilon,\zeta$ -unsaturated nitrones as exemplified by the reaction of citronellal with *N*-methylhydroxylamine (Eq. 12).<sup>274</sup>



The stereochemistry of these cycloadditions has been rigorously investigated and it is found that cyclization at 76°C gives primarily the *trans*-fused isomers, the *cis*-*trans* isomer ratio being influenced mainly by substituents in the isoxazoline ring. In the temperature range 180–300°C interconversion

<sup>272</sup> P. Bravo, G. Gaudino, P. P. Ponti, and C. Ticozzi, *Tetrahedron* **28**, 3845 (1972).

<sup>273</sup> R. Jacquier, C. Petrus, F. Petrus, and J. Verducci, *Bull. Soc. Chim. Fr.* 2690 (1970).

<sup>274</sup> N. A. LeBel and D. Hwang, *Org. Synth.* **58**, 106 (1978); N. A. LeBel and E. Banucci, *J. Am. Chem. Soc.* **92**, 5278 (1970).

of the isomers takes place by a retro-1,3-dipolar cycloaddition, the cis-fused isomer predominating.<sup>275</sup>

N-Alkyloctahydroanthranils on photolysis or on treatment with strong base ring-expand to perhydrobenzo-3,1-oxazines.<sup>276</sup>

## H. USES

3-( $\omega$ -Alkylamino)anthranils having central nervous system depressant, muscle relaxing, neuroleptic, vasodilatory, antiasthmatic, and platelet anti-coagulating activity, are to be found in the patent literature.<sup>277</sup>

3-Methylanthranil, *in vitro*, is 1000 times more active than isoxazole as an inhibitor of monoamine oxidase.<sup>278</sup> N-Alkylanthranilium salts are useful intermediates in the synthesis of benzodiazepin-2-ones.<sup>279</sup>

4,6-Dinitroanthranil is thought to be the autocatalyst in the thermal decomposition of TNT.<sup>280</sup>

1-Acylbenzisoxazolin-3-one-4-carboxylic acids have found use as hair dyes<sup>281</sup> and photographic diffusion-transfer color couplers.<sup>282</sup> Some 1-(aminoalkyl)benzisoxazolines have tranquilizer activity.<sup>283</sup>

<sup>275</sup> N. A. LeBel and T. A. Lajiness, *Tetrahedron Lett.*, 2173 (1966); N. A. LeBel and E. G. Banucci, *J. Org. Chem.* **36**, 2440 (1971).

<sup>276</sup> N. A. LeBel, T. A. Lajiness, and D. B. Ledlie, *J. Am. Chem. Soc.* **89**, 3076 (1967).

<sup>277</sup> J. Katsube, T. Kobayashi, K. Tamoto, Y. Takebayashi, K. Sasajima, S. Inaba, and H. Yamamoto, Ger. Offen. 2,529,292 (1976) [*CA* **84**, 135627 (1976)]; Japan Kokai 77/83,741 [*CA* **88**, 37781 (1978)]; British Patent 1,502,384 (1978) [*CA* **89**, 109444 (1978)].

<sup>278</sup> A. G. Bolt, P. B. Ghosh, and M. J. Sleight, *Biochem. Pharmacol.* **23**, 1963 (1974).

<sup>279</sup> K. Shirakawa, O. Aki, K. Nakagawa, and M. Yamamoto, Japanese Patent 73/08,097 [*CA* **79**, 92197 (1973)].

<sup>280</sup> Y. Y. Maksimov, V. F. Sapranovich, and N. V. Polyakov, *Tr. Mosk. Khim.-Tekhnol. Inst.* **83**, 51 (1974) [*CA* **85**, 162845 (1976)].

<sup>281</sup> R. Rehberg, Ger. Offen. 1,921,325 (1970) [*CA* **74**, 24940 (1971)].

<sup>282</sup> J. C. Hinshaw and P. B. Condit, Ger. Offen. 2,628,044 (1977) [*CA* **87**, 103370 (1977)]; Ger. Offen. 2,628,043 (1976) [*CA* **87**, 93492 (1977)]; Ger. Offen. 2,402,900 (1974) [*CA* **81**, 179866 (1974)].

<sup>283</sup> Y. Nakagawa, O. Aki, and M. Yamamoto, Japan Kokai 73/68,565; [*CA* **79**, 137121 (1973)].

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# Advances in the Chemistry of Heteroaromatic N-Imines and N-Aminoazonium Salts

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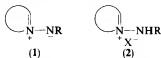
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## I. Introduction

It has become increasingly apparent that heteroaromatic *N*-imines **1** and their protonated compounds *N*-aminoazonium salts **2** are highly useful as synthetic intermediates, particularly in preparative heterocyclic chemistry.



Recently, efficient synthetic methods for this class of compounds have been developed so that a variety of such compounds are now readily available. The nucleophilicity of the imino or amino nitrogen, the electrophilicity of the heteroaromatic ring, and the dipolar character permit them to react in a number of ways, depending upon the nature of the heteroaromatic ring, substituents, the reagent, and the conditions.

Although aspects of the chemistry of the heteroaromatic *N*-imines have been reviewed several times,<sup>1-4</sup> recent significant developments in this field

<sup>1</sup> T. Okamoto and M. Hirobe, *Yuki Gosei Kagaku Kyokai Shi* **26**, 746 (1968).

<sup>2</sup> H.-J. Timpe, *Z. Chem.* **12**, 250 (1972); *Adv. Heterocycl. Chem.* **17**, 213 (1974).

<sup>3</sup> W. J. McKillip, E. A. Sedor, B. M. Culbertson, and S. Wawzonek, *Chem. Rev.* **73**, 255 (1973).

<sup>4</sup> C. G. Stuckwisch, *Synthesis*, 469 (1973).



necessitate a current review. This review covers the literature published during 1970 to early 1980, but some earlier relevant works are also included.

The nomenclature for the *N*-imines is varied; for example,  $C_5H_5N^+ - N^-COPh$  is named variously as pyridine *N*-(or 1-)-benzoylimine, pyridine *N*-(or 1-)-benzoylimide, *N*-(or 1-)-benzoyliminopyridinium ylide (or betaine), 1-benzoylaminopyridinium hydroxide, inner salt (*Chemical Abstracts*), or *N*-pyridiniobenzamdate (IUPAC rule). The *N*-imine nomenclature will be used in this review.

## II. Preparation

The synthetically important methods can be classified into the following three categories: (i) direct *N*-amination of the heteroaromatic bases, (ii) cyclization of monohydrazone derivatives, and (iii) *N*-alkylation of *N*-aminoazoles. In addition, there are several special methods that have been used for the preparation of some particular heteroaromatic *N*-imines and *N*-aminoazonium salts.

### A. PREPARATION BY DIRECT *N*-AMINATION

The most general preparations are based on the reaction of the heteroaromatic bases with *O*-substituted hydroxylamines. An alternative but less efficient method is the reaction of heteroaromatic bases with nitrenes generated from acyl and sulfonyl azides.

#### 1. *N*-Amination by Hydroxylamine Derivatives

The most commonly used hydroxylamine derivatives are hydroxylamine *O*-sulfonic acid (HSA) (3) (or its alkali salts)<sup>5</sup> and *O*-mesitylenesulfonylhydroxylamine (MSH) (4).<sup>6,7</sup> Although HSA is more easily and cheaply prepared, it presents solubility problems (it is water-soluble but insoluble in most organic solvents except methanol and diglyme). In addition, it has rather weak aminating power and limited application: the *N*-amination reaction fails with pyridines bearing electron-withdrawing substituents (e.g.,

<sup>5</sup> R. Gösl and A. Meuwesen, *Chem. Ber.* **92**, 2521 (1959); *Org. Synth.* **43**, 1 (1963); R. G. Wallace, *Aldrichimica Acta* **13**, 3 (1980).

<sup>6</sup> Y. Tamura, J. Minamikawa, Y. Miki, S. Matsugashita, and M. Ikeda, *Tetrahedron Lett.*, 4133 (1972).

<sup>7</sup> Y. Tamura, J. Minamikawa, K. Sumoto, S. Fujii, and M. Ikeda, *J. Org. Chem.* **38**, 1239 (1973).

CO<sub>2</sub>Et, CN, NO<sub>2</sub>),<sup>8</sup> and abnormal reactions have been reported for 4-methoxypyridine,<sup>8</sup> pyrimidines,<sup>9</sup> quinolines,<sup>10</sup> quinazolines,<sup>11</sup> and acridines.<sup>12</sup> Despite these disadvantages, this method has been used for the synthesis of many heteroaromatic N-aminoazonium salts.<sup>5,8,9,13-22</sup>

Perhaps the most efficient method for the preparation of the N-aminoazonium salts is that using MSH.<sup>23</sup> This rather new procedure has been shown to have many advantages over the other known methods: (i) the procedure is very simple, (ii) the reaction conditions are extremely mild, (iii) the scope is wide (i.e., it appears to parallel closely that of N-oxidation by peracids<sup>24</sup>), and (iv) the yields are generally high. Recent applications of MSH (after 1976; for earlier applications, see Ref. 23) include pyridines,<sup>25-28</sup> quinolines,<sup>29-31</sup> naphthyridines,<sup>32</sup> fused pyridines,<sup>32</sup> phenanthridines,<sup>33,34</sup>

<sup>8</sup> J. Epszajn, E. Lunt, and A. R. Katritzky, *Tetrahedron* **26**, 1665 (1970).

<sup>9</sup> K. Kasuga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 1814 (1974).

<sup>10</sup> M. H. Palmer and P. S. McIntyre, *Tetrahedron Lett.*, 2147 (1968).

<sup>11</sup> K. Kasuga, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi* **94**, 945 (1974) [*CA* **81**, 136093 (1974)].

<sup>12</sup> T. Ozawa, Y. Iitaka, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 2069 (1974).

<sup>13</sup> T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *Yakugaku Zasshi* **83**, 308 (1963) [*CA* **59**, 5130 (1963)].

<sup>14</sup> T. Okamoto, M. Hirobe, and T. Yamazaki, *Chem. Pharm. Bull.* **14**, 512 (1966).

<sup>15</sup> A. Ohsawa, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi* **92**, 73 (1972) [*CA* **76**, 126730 (1972)].

<sup>16</sup> S. Suzue, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi* **93**, 1331 (1973) [*CA* **80**, 47799 (1974)].

<sup>17</sup> R. Huisgen, R. Grashey, and R. Krischke, *Justus Liebigs Ann. Chem.*, 506 (1977).

<sup>18</sup> K. T. Potts, U. P. Singh, and J. Bhattacharyya, *J. Org. Chem.* **33**, 3766 (1968).

<sup>19</sup> E. E. Glover and M. Yorke, *J. C. S. Perkin I*, 3280 (1971).

<sup>20</sup> T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *J. Org. Chem.* **35**, 426 (1970).

<sup>21</sup> A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.* **35**, 433 (1970).

<sup>22</sup> M. Sainsbury, B. Webb, and R. Schinazi, *J. C. S. Perkin I*, 289 (1975).

<sup>23</sup> Y. Tamura, J. Minamikawa, and M. Ikeda, *Synthesis*, 1 (1977).

<sup>24</sup> A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," p. 22. Academic Press, New York, 1971.

<sup>25</sup> M. Sainsbury and R. F. Schinazi, *J. C. S. Perkin I*, 1155 (1976).

<sup>26</sup> M. Driver and M. Sainsbury, *J. C. S. Perkin I*, 2502 (1979).

<sup>27</sup> A. Frankowski and J. Streith, *Tetrahedron* **33**, 427 (1977).

<sup>28</sup> H. Fritz, R. Gleiter, M. Nastasi, J.-L. Schuppiser, and J. Streith, *Helv. Chim. Acta* **61**, 2887 (1978).

<sup>29</sup> T. Tsuchiya, J. Kurita, and V. Snieckus, *J. Org. Chem.* **42**, 1856 (1977).

<sup>30</sup> Y. Tamura, Y. Miki, H. Hayashi, Y. Sumida, and M. Ikeda, *Heterocycles* **6**, 281 (1977).

<sup>31</sup> B. Ágai and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **86**, 203 (1975).

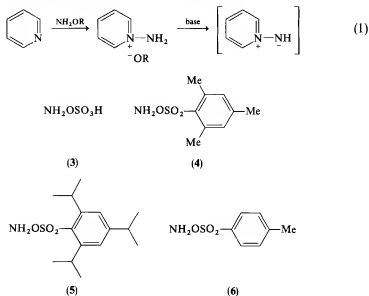
<sup>32</sup> T. Tsuchiya, M. Enkaku, J. Kurita, and H. Sawanishi, *Chem. Pharm. Bull.* **27**, 2183 (1979).

<sup>33</sup> Y. Tamura, Y. Miki, Y. Nishikawa, and M. Ikeda, *J. Heterocycl. Chem.* **13**, 317 (1976).

<sup>34</sup> B. Ágai, K. Lempert, and J. Hegedüs-Vajda, *Acta Chim. Acad. Sci. Hung.* **91**, 91 (1976).

acridines,<sup>35</sup> diazines,<sup>31</sup> pyrazoles,<sup>36,37</sup> indazoles,<sup>36</sup> fused imidazoles,<sup>38,39</sup> and fused triazoles.<sup>39</sup>

Other hydroxylamine derivatives that can be used for the *N*-amination include the slightly less reactive *O*-2,4,6-triisopropylbenzenesulfonylhydroxylamine (**5**)<sup>7</sup> and the less stable *p*-toluenesulfonylhydroxylamine (**6**).<sup>39-42</sup> Chloramine (NH<sub>2</sub>Cl) cannot be used for this purpose.<sup>43</sup>



The *N'*-unsubstituted *N*-imines are usually generated *in situ* by treatment of the *N*-aminoazonium salts with base and used directly for subsequent reactions because of the instability of the *N*-imines (Eq. 1). Some *N*-imines such as quinoline, isoquinoline, and phenanthridine *N*-imines are known to form crystalline dimers,<sup>17</sup> which are in equilibrium with the *N*-imines in solutions.<sup>29</sup> The only exception is benzo[*c*]cinnoline *N*-imine which is isolable as a stable crystalline solid.<sup>44</sup>

<sup>35</sup> B. Ágai and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **88**, 75 (1976).

<sup>36</sup> H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **24**, 2267 (1976).

<sup>37</sup> H. Koga, M. Hirobe, and T. Okamoto, *Tetrahedron Lett.*, 1291 (1978).

<sup>38</sup> E. E. Glover and K. D. Vaughan, *J. C. S. Perkin I*, 1137 (1974).

<sup>39</sup> E. E. Glover and K. T. Rowbottom, *J. C. S. Perkin I*, 367 (1976).

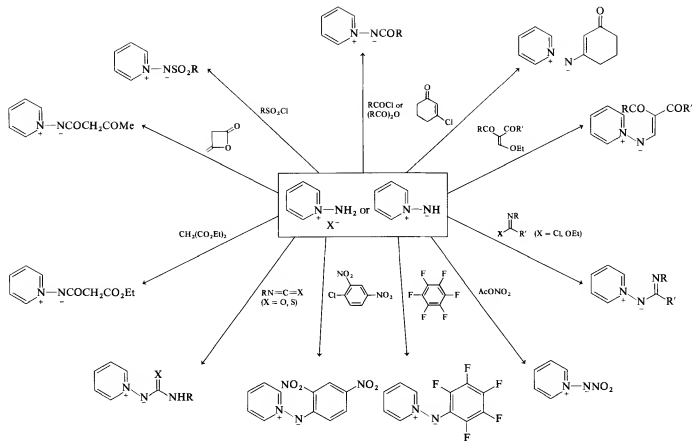
<sup>40</sup> D. G. Doughty, E. E. Glover, and K. D. Vaughan, *J. C. S. Perkin I*, 78 (1977).

<sup>41</sup> D. G. Doughty and E. E. Glover, *J. C. S. Perkin I*, 1593 (1977).

<sup>42</sup> J. T. Boyers and E. E. Glover, *J. C. S. Perkin I*, 1960 (1977).

<sup>43</sup> M. E. Brooks and B. Rudner, *J. Am. Chem. Soc.* **78**, 2339 (1956).

<sup>44</sup> S. F. Gait, M. E. Peek, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 19 (1975).



SCHEME 1

The *N'*-substituted *N*-imines can be prepared by the reaction of the *N*-aminoazonium salts, in the presence or absence of base, with anhydrides or acyl halides,<sup>8,13-17,20,21,45,46</sup> diketene,<sup>47</sup> diethyl malonate,<sup>48</sup> sulfonyl chloride,<sup>8,15,49,50</sup>  $\beta$ -halovinyl ketones and esters,<sup>51-54</sup> diethyl ethoxymethylenemalonate and related compounds,<sup>53,55-57</sup> isocyanates,<sup>17,58</sup> thioisocyanates,<sup>17,58</sup> imidooyl chlorides and imidates,<sup>59,60</sup> nitro acetate,<sup>8,61</sup> and active halobenzenes.<sup>62,63</sup> Some representative pyridine *N*-(substituted imines) prepared in this way are shown in Scheme 1.

## 2. *N*-Amination by Nitrenes

Nitrenes generated photochemically or thermally from arenesulfonyl azides and alkoxycarbonyl azides add to the nitrogen atom of heteroaromatic bases to give the corresponding *N*-(substituted imines).<sup>20,21,50,64-69</sup> However, the yields are usually low and the scope is severely limited.

<sup>45</sup> T. Okamoto, M. Hirobe, and A. Ohsawa, *Chem. Pharm. Bull.*, **14**, 518 (1966).

<sup>46</sup> J. W. Lown and K. Matsumoto, *Can. J. Chem.*, **50**, 584 (1972).

<sup>47</sup> T. Kato and S. Masuda, *Chem. Pharm. Bull.*, **23**, 452 (1975).

<sup>48</sup> A. Kakehi, S. Ito, Y. Konno, and T. Maeda, *Bull. Chem. Soc. Jpn.*, **51**, 251 (1978).

<sup>49</sup> M. Ikeda, S. Kato, Y. Sumida, and Y. Tamura, *Org. Mass Spectrum.*, **5**, 1383 (1971).

<sup>50</sup> R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).

<sup>51</sup> Y. Tamura, N. Tsujimoto, and M. Ikeda, *Chem. Commun.*, 310 (1971).

<sup>52</sup> Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, *Tetrahedron*, **28**, 21 (1971).

<sup>53</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **37**, 3106 (1972).

<sup>54</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron Lett.*, 5245 (1972).

<sup>55</sup> Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. C. S. Perkin I*, 2580 (1973).

<sup>56</sup> A. Kakehi, S. Ito, T. Funakoshi, and Y. Ota, *J. Org. Chem.*, **41**, 1570 (1976).

<sup>57</sup> H. Fujito, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles*, **6**, 379 (1977).

<sup>58</sup> R. Kriskche, R. Grashey, and R. Huisgen, *Justus Liebigs Ann. Chem.*, 498 (1977).

<sup>59</sup> A. Kakehi, S. Ito, K. Uchiyama, and Y. Konno, *Chem. Lett.*, 413 (1976).

<sup>60</sup> A. Kakehi, S. Ito, K. Uchiyama, Y. Konno, and K. Kondo, *J. Org. Chem.*, **42**, 443 (1977).

<sup>61</sup> J. Epszajn, A. R. Katritzky, E. Lunt, J. W. Mitchell, and G. Roch, *J. C. S. Perkin I*, 2622 (1973).

<sup>62</sup> T. Okamoto, S. Hayashi, H. Horikiri, and M. Hirobe, *Yakugaku Zasshi*, **91**, 210 (1971) [*CA* **74**, 99818 (1971)].

<sup>63</sup> R. E. Banks and S. M. Hitchen, *J. Fluorine Chem.*, **12**, 159 (1978).

<sup>64</sup> D. S. Breslow, in "Nitrenes" (W. Lwowski, ed.), p. 245. Wiley (Interscience), New York, 1970.

<sup>65</sup> B. Ágai, K. Lempert, and J. Möller, *Acta Chim. Acad. Sci. Hung.*, **80**, 465 (1974).

<sup>66</sup> K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Lett.*, 1733 (1964).

<sup>67</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36**, 2978 (1971).

<sup>68</sup> J. Streith and J. M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).

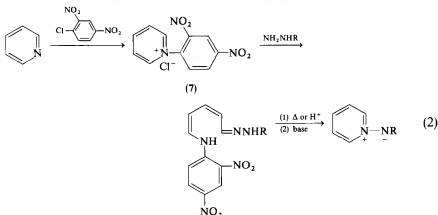
<sup>69</sup> J. Streith, T. P. Luttringer, and M. Nastasi, *J. Org. Chem.*, **36**, 2962 (1971).

## B. PREPARATION BY CYCLIZATION

The synthesis of heteroaromatic *N*-imines by way of ring opening of *N*-(2,4-dinitrophenyl)pyridinium chlorides or pyrylium salts with hydrazine derivatives followed by recyclization has been known for many years. In particular, the latter procedure was the first method to be discovered for preparing pyridine *N*-imines.<sup>70</sup>

1. Preparation from *N*-(2,4-Dinitrophenyl)pyridinium Chlorides and Hydrazine Derivatives

*N*-(2,4-Dinitrophenyl)pyridinium chlorides ("Zincke salts") (7), readily prepared from pyridines and 2,4-dinitrochlorobenzene, react with hydrazine and monosubstituted hydrazines to give 5-(2,4-dinitroanilino)-2,4-pentadienal monohydrazones. On refluxing in dioxane-water (4:1) or on treating with acid, the hydrazones undergo recyclization to give the corresponding *N*-imines (Eq. 2). This method can be applied to pyridine,<sup>71-74</sup> 3-substituted (except the strong electron-withdrawing groups) pyridines,<sup>8,75-77</sup> 4-alkylpyridines,<sup>75-77</sup> and isoquinoline.<sup>71,78,79</sup>



<sup>70</sup> W. Schneider and F. Seebach, *Ber. Dtsch. Chem. Ges.* **54**, 2285 (1921).

<sup>71</sup> H. Beyer and E. Thieme, *J. Prakt. Chem.* [2] **31**, 293 (1966).

<sup>72</sup> Y. Tamura and N. Tsujimoto, *Chem. Ind. (London)*, 926 (1970).

<sup>73</sup> E. E. Knaus and K. Redda, *J. Heterocycl. Chem.* **13**, 1237 (1976).

<sup>74</sup> C. Leonte and E. Carp, *Rev. Roum. Chim.* **23**, 1461 (1978).

<sup>75</sup> Y. Tamura, N. Tsujimoto, and M. Mano, *Chem. Pharm. Bull.* **19**, 130 (1971).

<sup>76</sup> Y. Tamura, N. Tsujimoto, and M. Uchimura, *Yakugaku Zasshi* **91**, 72 (1971) [*CA* **74**, 99804 (1971)].

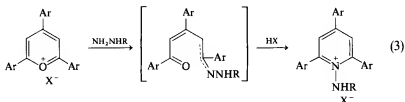
<sup>77</sup> Y. Tamura, Y. Miki, T. Honda, and M. Ikeda, *J. Heterocycl. Chem.* **9**, 865 (1972).

<sup>78</sup> Y. Tamura, N. Tsujimoto, and M. Uchimura, *Chem. Pharm. Bull.* **19**, 143 (1971).

<sup>79</sup> B. Agai and K. Lempert, *Tetrahedron* **28**, 2069 (1972).

## 2. Preparation from Pyrylium Salts and Hydrazine Derivatives

Pyrylium salts also react with hydrazine and its derivatives to give the *N*-aminoazonium salts (Eq. 3), although the reaction takes other courses in some cases.<sup>50,70,80-93</sup> The reaction involves the formation of intermediate hydrazones by nucleophilic attack at the  $\alpha$ -position of pyrylium rings. The hydrazones undergo ring closure followed by dehydration. This method has been utilized for the preparation of highly substituted pyridine *N*-imines.



## 3. Miscellaneous Ring Closures

Although several special routes have been reported,<sup>19,39,94-106</sup> only a few examples are shown here: (i) the synthesis of isoquinoline *N*-imines by base-induced cyclization of sulfonyl- and acylhydrazones of 2-ethynyl-

<sup>80</sup> A. T. Balaban, W. Schroth, and G. Fischer, *Adv. Heterocycl. Chem.* **10**, 241 (1969).

<sup>81</sup> H. Perst, "Oxonium Ions in Organic Chemistry," p. 149. Academic Press, New York, 1971.

<sup>82</sup> H. C. van Der Plas, "Ring Transformations of Heterocyclic Compounds," Vol. 2, p. 1. Academic Press, New York, 1973.

<sup>83</sup> A. T. Balaban, *Tetrahedron* **24**, 5059 (1968).

<sup>84</sup> M. Lempert-Sréter and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **65**, 443 (1970).

<sup>85</sup> M. Lempert-Sréter and K. Lempert, *Acta Chim. Acad. Sci. Hung.* **88**, 189 (1976).

<sup>86</sup> R. Neidlein and P. Witerzens, *Arch. Pharm. (Weinheim, Ger.)* **309**, 649 (1976).

<sup>87</sup> J. B. Bapat, R. J. Blade, A. J. Boulton, J. Epszajn, A. R. Katritzky, J. Lewis, P. Molina-Buendia, P.-L. Nie, and C. A. Ramsden, *Tetrahedron Lett.*, 2691 (1976).

<sup>88</sup> A. R. Katritzky, J. Lewis, and P.-L. Nie, *J. C. S. Perkin I*, 446 (1979).

<sup>89</sup> A. R. Katritzky, P.-L. Nie, A. Dondoni, and D. Tassi, *Synth. Commun.* **7**, 387 (1977).

<sup>90</sup> A. R. Katritzky, P.-L. Nie, A. Dondoni, and D. Tassi, *J. C. S. Perkin I*, 1961 (1979).

<sup>91</sup> E. A. Zvezdina, M. P. Zhdanova, and G. N. Dorofeenko, *Khim. Geterotsikl. Soedin.*, 324 (1979).

<sup>92</sup> V. Snieckus and G. Kan, *Chem. Commun.*, 1208 (1970).

<sup>93</sup> D. J. Harris, G. Y.-P. Kan, T. Tschamber, and V. Snieckus, *Can. J. Chem.* **58**, 494 (1980).

<sup>94</sup> P. N. Anderson and J. T. Sharp, *J. C. S. Perkin I*, 1331 (1980).

<sup>95</sup> C. S. Angadiyavar, K. B. Sukumaran, and M. V. George, *Tetrahedron Lett.*, 633 (1971).

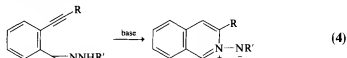
<sup>96</sup> K. B. Sukumaran, C. S. Angadiyavar, and M. V. George, *Tetrahedron* **28**, 3987 (1972).

<sup>97</sup> K. B. Sukumaran, S. Satish, and M. V. George, *Tetrahedron* **30**, 445 (1974).

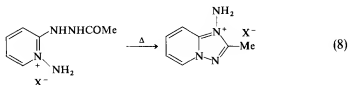
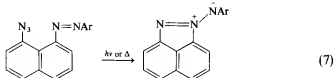
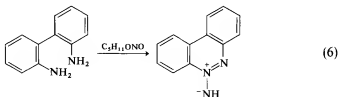
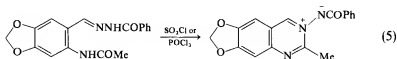
<sup>98</sup> H. Bauer, G. R. Bedford, and A. R. Katritzky, *J. Chem. Soc.*, 751 (1964).

<sup>99</sup> G. V. Boyd and A. J. H. Summers, *J. Chem. Soc. C*, 409 (1971).

benzaldehydes<sup>94</sup> (Eq.4), (ii) the synthesis of quinazoline 3-acylimines from hydrazone derivatives of *o*-acylaminobenzaldehydes (Eq. 5),<sup>100</sup> (iii) the synthesis of benzo[*c*]cinnoline *N*-imines from various biphenyl derivatives (Eq. 6),<sup>101-105</sup> (iv) the formation of benz[*cd*]indazole *N*-arylimines by thermolysis or photolysis of 8-azido-1-arylazonaphthalenes (Eq. 7),<sup>106</sup> and (v) the formation of 1-aminotriazolopyridinium salts from the 2-(2-acylhydrazino)-1-aminopyridinium salts via acyl migration (Eq. 8).<sup>39</sup>



R = H, Ph; R' = Ts, C<sub>6</sub>H<sub>5</sub>, etc.



<sup>100</sup> J. Fetter, K. Lempert, and J. Möller, *Tetrahedron* **31**, 2559 (1975).

<sup>101</sup> S. F. Gait, C. W. Rees, and R. C. Storr, *Chem. Commun.*, 1545 (1971).

<sup>102</sup> S. F. Gait, M. E. Peek, C. W. Rees, and R. C. Storr, *J. C. S. Chem. Commun.*, 982 (1972).

<sup>103</sup> S. F. Gait, M. E. Peek, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 1248 (1974).

<sup>104</sup> F. A. Neugebauer and H. Fischer, *Chem. Ber.* **106**, 1589 (1973).

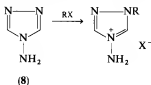
<sup>105</sup> P. Spagnolo, A. Tundo, and P. Zanirato, *J. Org. Chem.* **42**, 292 (1977).

<sup>106</sup> P. Spagnolo, A. Tundo, and P. Zanirato, *J. Org. Chem.* **43**, 2508 (1978).



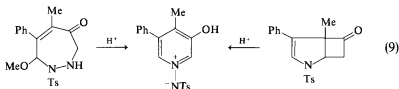
C. PREPARATION BY ALKYLATION OF *N*-AMINOAZOLES

Alkylation of the readily accessible 1-aminoimidazoles,<sup>107</sup> 1-amino-benzimidazoles,<sup>108</sup> 1-aminotriazoles<sup>8, 109–114</sup> and 1-aminobenzotriazoles<sup>113</sup> gives the corresponding *N*-aminoazonium salts in good yields.



## D. MISCELLANEOUS METHODS

The formation of pyridine *N*-imines by an acid-catalyzed rearrangement of some diazepinones and related compounds has been extensively investigated by Moore and co-workers (Eq. 9).<sup>115</sup> The formation of pyridine *N*-imines from 1*H*-1,2-diazepines is also known (Eq. 10).<sup>68, 69, 116, 117</sup> Diels-Alder reactions of pyrazoles with dimethyl acetylenedicarboxylate, in the presence of BF<sub>3</sub>, have been reported to give *N*-aminopyridinium salts (Eq. 11).<sup>118</sup> 1,4-Dihydropyrido[1,2-*a*]-as-triazinium salts and their pyrimido derivatives undergo ring contraction in boiling aqueous acid, yielding 1-aminoimidazo[1,2-*a*]pyridinium and pyrimidinium salts, respectively (Eq. 12).<sup>40, 119</sup>



<sup>107</sup> E. E. Glover, K. T. Rowbottom, and D. C. Bishop, *J. C. S. Perkin I*, 2927 (1972).

<sup>108</sup> E. E. Glover, K. T. Rowbottom, and D. C. Bishop, *J. C. S. Perkin I*, 842 (1973).

<sup>109</sup> H. G. O. Becker, N. Sauder, and H.-J. Timpe, *J. Prakt. Chem.* [2] **311**, 897 (1969).

<sup>110</sup> H. G. O. Becker and H.-J. Timpe, *J. Prakt. Chem.* [2] **312**, 1112 (1970).

<sup>111</sup> H. G. O. Becker, K. Heimburger, and H.-J. Timpe, *J. Prakt. Chem.* [2] **313**, 795 (1971).

<sup>112</sup> H. G. O. Becker, H. D. Steinleitner, and H.-J. Timpe, *Synthesis*, 414 (1973).

<sup>113</sup> E. E. Glover and K. T. Rowbottom, *J. C. S. Perkin I*, 1792 (1974).

<sup>114</sup> A. R. Katritzky and J. W. Mitchell, *J. C. S. Perkin I*, 2624 (1973).

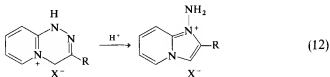
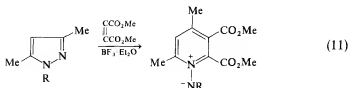
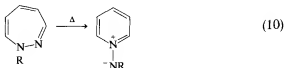
<sup>115</sup> J. A. Moore, W. J. Volker, and C. M. Kopay, *J. Org. Chem.* **36**, 2676 (1971), and earlier papers

<sup>116</sup> G. Kan, M. T. Thomas, and V. Snieckus, *Chem. Commun.*, 1022 (1971).

<sup>117</sup> D. J. Harris, M. T. Thomas, V. Snieckus, and E. Klingsberg, *Can. J. Chem.* **52**, 2805 (1974).

<sup>118</sup> F. Abjean, *C. R. Acad. Sci., Ser. C* **278**, 359 (1974).

<sup>119</sup> C. K. Bradsher, R. D. Brandau, J. E. Boliek, and T. L. Hough, *J. Org. Chem.* **34**, 2129 (1969).



### III. Physical Properties

#### A. CRYSTAL AND ELECTRONIC STRUCTURES

An X-ray crystal structure analysis has been reported for pyridine *N*-nitroimine.<sup>120</sup> The  $\text{N}^+(1)-\text{N}^-(2)-\text{N}(3)\text{O}_2$  system of the *N*-imine is almost planar, but at a dihedral angle of  $71.7^\circ$  to the ring plane. The ring dimensions are in good agreement with those found in pyridine *N*-oxide, but compared with  $\text{Me}_3\text{N}^+-\text{N}^-\text{NO}_2$  there is a significant shortening of the  $\text{N}(1)-\text{N}(2)$  bond, a lengthening of  $\text{N}(2)-\text{N}(3)$ , and a decrease in the  $\text{N}(1)-\text{N}(2)-\text{N}(3)$  angle.

A CNDO/2 molecular orbital calculation for pyridine *N*-nitroimine has been performed, and the total charge distribution is compared with that for pyridine *N*-oxide.<sup>120</sup>

#### B. PHOTOELECTRON SPECTRA

The X-ray photoelectron spectra of pyridine *N*-acylimines and *N*-arene-sulfonylimines have been measured.<sup>121</sup> The binding energies of the 1s electrons of their nitrogen atoms (396.4 eV for the imino nitrogen atom and

<sup>120</sup> J. Arriau, J. Deschamps, J. R. C. Duke, J. Epszajn, A. R. Katritzky, E. Lunt, J. W. Mitchell, S. Q. A. Rizvi, and G. Roch, *Tetrahedron Lett.*, 3865 (1974).

<sup>121</sup> J. P. Catteau, A. Lablache-Combiér, J. Grimblot, M. Nastasi, and J. Streith, *Tetrahedron* **31**, 2909 (1975).

400 eV for the ring nitrogen atom) show that the negative charge remains, to a large extent, on the imino nitrogen atom, whereas the positive charge on the ring nitrogen is delocalized on the pyridine ring with higher positive charge density at the 2- and 6-positions. This is in accord with the reactivity of the *N*-imines as 1,3-dipoles.

### C. INFRARED SPECTRA

General discussions of the infrared (IR) spectra of *N'*-substituted *N*-imines have been given in the earlier reviews.<sup>1-3</sup> *N*-Acylimines show the carbonyl stretching band at 1530–1650 cm<sup>-1</sup>, depending upon the nature of the acyl group.<sup>13,20,21,51,52,69,77,109,122</sup> These values are generally about 100 cm<sup>-1</sup> lower than in the corresponding amides. The lowering of frequency is also observed in *N*-nitroimines (1380–1415 and 1260–1300 cm<sup>-1</sup>)<sup>61,123,124</sup> and *N*-sulfonylimines (1270–1285 and 1130–1140 cm<sup>-1</sup>).<sup>50,110</sup> These results provide good evidence for the delocalization of the negative charge.

### D. ULTRAVIOLET SPECTRA

The ultraviolet (UV) absorption spectra of the heteroaromatic *N*-imines are dependent upon many factors, such as the nature of the parent heterocycles, substituents on the imino nitrogen, and solvent used. Usually pyridine *N*-acylimines show two intense absorption maxima at 230–235 and 330–360 nm in aprotic solvents such as dioxane, benzene, or chloroform, the latter band of which disappears by addition of acid.<sup>13,20,21,75,77</sup> In protic solvents such as alcohol or water a hypsochromic shift and a hypochromic effect of the long-wavelength absorption are observed: for example, pyridine *N*-benzoylimine shows a maximum at 352 nm ( $\epsilon$  9700) in dioxane but at 313 nm ( $\epsilon$  4650) in ethanol.<sup>13,21</sup> The long-wavelength absorption of pyridine *N*-ethoxycarbonylimine has been ascribed to a  $\pi$ - $\pi^*$  transition on the basis of a Pariser-Parr-Pople (PPP) calculation and measurements of the absorption spectra of preoriented pyridine *N*-imines in polarized UV light.<sup>125</sup>

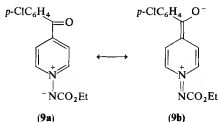
An acyl substituent at the 4-position of the pyridine ring has a considerable bathochromic effect: for example, 4-(*p*-chlorobenzoyl)pyridine *N*-ethoxycarbonylimine (**9**) shows an absorption maximum at 395 nm (in benzene). This suggests considerable contribution of a structure such as **9b** to the resonance hybrid.<sup>21</sup>

<sup>122</sup> Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 781 (1974).

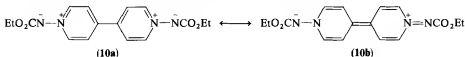
<sup>123</sup> J. Epszajn and A. R. Katritzky, *Tetrahedron Lett.*, 4739 (1969).

<sup>124</sup> H.-J. Timpe, *Z. Chem.* **11**, 340 (1971).

<sup>125</sup> R. Gleiter, D. Schmidt, and J. Streith, *Helv. Chim. Acta* **54**, 1645 (1971).



The absorption maximum of 4,4'-bipyridine *N,N'*-dibenzoylimine (**10**) appears at 391 nm (in dioxane), suggesting the existence of an appreciable electronic interaction between two pyridine rings (see **10b**).<sup>126</sup>



Pyridine *N*-sulfonylimines show UV spectra similar to those of the *N*-acylimines.<sup>127</sup>

The *N*-acylimines of the five-membered heterocycles also have a long-wavelength absorption but at lower wavelengths than the pyridine cases: 250–285 nm (in chloroform) for 1-alkylimidazole 3-acylimines and 300–320 nm (in chloroform) for 1-alkylbenzimidazole 3-acylimines.<sup>122</sup> Solvent effect on the UV spectra of 1-alkyl-1,2,4-triazole 4-acylimines has been discussed.<sup>128</sup>

## E. NUCLEAR MAGNETIC RESONANCE SPECTRA

The complete analysis of <sup>1</sup>H-NMR spectra of a series of *N'*- and 3-substituted pyridine *N*-imines has been reported.<sup>129</sup> The chemical shifts ( $\delta$ ) of the ring protons for pyridine *N*-imines decrease in the order H-2 (H-6) > H-4 > H-3 (H-5). A similar relationship is seen in the <sup>13</sup>C-NMR spectrum of pyridine *N*-benzoylimine which indicates significant downfield shifts of C-2 (143.1 ppm) and C-4 (137.8 ppm) relative to C-3 (129.4 ppm), reflecting the electron density at these positions.<sup>130</sup>

The <sup>1</sup>H-NMR spectra have been used to assign the structures of benzo-diazine *N*-imines obtained by direct amination in which two isomeric

<sup>126</sup> Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **10**, 447 (1972).

<sup>127</sup> R. A. Abramovitch and T. Takaya, *J. Org. Chem.* **38**, 3311 (1973).

<sup>128</sup> H.-J. Timpe and H. G. O. Becker, *Chimia* **26**, 473 (1972).

<sup>129</sup> A. R. Katritzky, M. Kinns, and E. Lunt, *Org. Magn. Reson.* **7**, 569 (1975).

<sup>130</sup> S. A. Dias, A. W. Downs, and W. R. McWhinnie, *J. C. S. Dalton*, 162 (1975).

products could be formed.<sup>131</sup> This method is based on the fact that the conversion of the heteroaromatic amines into the *N*-amine salts or *N*-benzoylimines produces a considerable downfield shift of H-2 in quinoline-type compounds and H-1 in isoquinoline-type compounds.

<sup>1</sup>H-NMR spectroscopy has been used to particular advantage in determining the  $pK_a$  value of the unisolable pyridine *N'*-unsubstituted *N*-imine which has a very high  $pK_a$  value (13.4).<sup>8</sup>

The <sup>1</sup>H-NMR spectra of 1-alkylbenzimidazole *N*-acylimines have been compared with those of the corresponding *N*-oxides and related compounds.<sup>122</sup> The <sup>1</sup>H-NMR spectra of 1-alkyl-1,2,4-triazole *N*-imines have also been discussed.<sup>2,132</sup>

## F. MASS SPECTRA

The positive ion mass spectra of pyridine *N'*-unsubstituted *N*-imines, generated within the ion source by pyrolysis of the corresponding hydrochlorides, have been investigated.<sup>133</sup> The mass spectrum of pyridine *N*-imine contains peaks attributable to the loss of 15 (NH) and 16 (NH<sub>2</sub>) mass units from the molecular ion in a ratio of approximately 2.5:1, whereas introduction of a methyl group at the 2-position of the pyridine ring causes a significant change in the intensity ratio of the  $[M - NH]^+$  and  $[M - NH_2]^+$  (~1:2.5). This can be attributed to the operation of a so-called "ortho effect," as in the case of 2-alkylated pyridine *N*-oxides.

Major fragmentation of pyridine *N*-acylimines can be rationalized in terms of charge localization on the pyridine ring nitrogen.<sup>134</sup> With the exception of the *N*-ethoxycarbonylimines, *N*-acylimines usually give  $[M - 1]$  ions. Particularly in the *N*-benzoylimines, the  $[M - 1]$  ions greatly exceed the molecular ions in intensity. The origin of the eliminated hydrogen has been established by deuterium labeling experiments. The resulting fragment ion is best represented by a fully aromatized structure **a**. This observation has been used in determining the structures of benzodiazine *N*-imines formed by direct amination where two isomeric products could be obtained.<sup>131</sup>

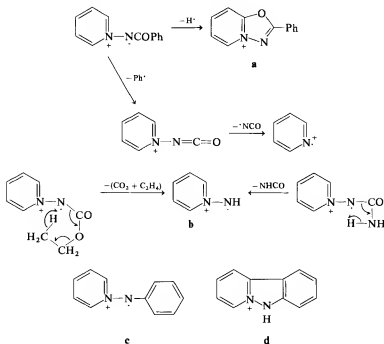
The most important primary fragmentation process of the *N*-acylimines is  $\alpha$ -cleavage of the molecular ion as indicated in Scheme 2. This ion decomposes further by elimination of NCO to furnish an ion-radical of the parent heterocycles.<sup>134</sup>

<sup>131</sup> Y. Tamura, Y. Miki, J. Minamikawa, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 675 (1974).

<sup>132</sup> G. V. Boyd and A. J. H. Summers, *J. Chem. Soc. B*, 1648 (1971).

<sup>133</sup> M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.* **5**, 935 (1971).

<sup>134</sup> M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.* **5**, 61 (1971).



SCHEME 2

The *N*-ethoxycarbonylimines and *N*-carbamoylimines lose  $\text{C}_2\text{H}_4 + \text{CO}_2$  and  $\text{HNCO}$ , respectively, to give pyridine *N*-imine ion-radical (**b**).<sup>134</sup>

The mass spectra of *N*-acylimines of quinoline,<sup>131</sup> isoquinoline,<sup>134</sup> benzodiazines,<sup>100,131</sup> and 1-alkylbenzimidazoles<sup>122</sup> also follow a similar fragmentation pattern. Interestingly, 1-alkyl-1,2,4-triazole 4-acylimines are reported to show no  $[\text{M} - 1]$  ions; the dominant primary fragmentation is cleavage of the  $\text{N}-\text{N}$  bond.<sup>135,136</sup>

The fragmentation of pyridine *N*-arenesulfonylimines is rather complicated. The most characteristic features are a very ready  $\text{N}-\text{S}$  bond cleavage and skeletal rearrangements. The latter processes involve the expulsion of  $\text{SO}_2$  from the molecular ion and the  $[\text{M} - 1]$  ion to give the corresponding ionized pyridine *N*-arylimines **c** and azacarbazoles **d**, respectively.<sup>49,127</sup>

The most prominent fragmentation process of pyridine *N*-arylimines is  $\text{N}-\text{N}$  bond cleavage with charge retention on both the pyridine and aryl fragments.<sup>137</sup>

<sup>135</sup> H. G. O. Becker, D. Beyer, and H.-J. Timpe, *Z. Chem.* **10**, 264 (1970).

<sup>136</sup> H.-J. Timpe, *J. Prakt. Chem.* [2] **315**, 775 (1973).

<sup>137</sup> M. Ikeda, N. Tsujimoto, and Y. Tamura, *Org. Mass Spectrom.* **5**, 389 (1971).

### G. DIPOLE MOMENTS

The dipole moments (in dioxane) of some isoquinoline *N*-acylimines (5.84 D for the *N*-phenylcarbamoylimine, 5.52 D for the *N*-ethoxycarbonylimine, and 6.20 D for the *N*-ethoxycarbonylacetylimine) have been reported.<sup>17</sup>

### H. ACID-BASE PROPERTIES

The basicity of *N*-imines depends upon the nature of the substituents on the imino nitrogen. Thus, pyridine *N'*-unsubstituted *N*-imine ( $pK_a$  11.2,<sup>138</sup> 13.6<sup>8</sup>) and *N*-methylimine ( $pK_a$  12–13<sup>138</sup>) are very strong bases, whereas pyridine *N*-acylimines ( $pK_a$  3.2 for the *N*-benzoylimine<sup>8</sup> and 3.6 for the *N*-acetylimine<sup>138</sup>) and *N*-nitroimine ( $pK_a$  –4.6<sup>8</sup>) are weak bases.

The protonation of pyridine *N*-nitroimine may occur at nitrogen or at oxygen. CNDO/2 calculations suggest the possibility of the latter.<sup>120</sup>

When treated with deuterium oxide, pyridine *N*-arylimines (at the 2- and 6-positions),<sup>137</sup> 1-alkyl-1,2,4-triazole 4-imines (at the 5-position),<sup>139</sup> and 1-alkylbenzimidazole 3-acylimines (at the 2-position)<sup>122</sup> undergo hydrogen-deuterium exchange at the specified position(s) shown in parentheses. The facility of the exchange in 1-methylbenzimidazole 3-acylimines decreases in the order 3-ethoxycarbonylimine > 3-acetylimine >> 3-benzoylimine, reflecting the electron-donating ability of the 3-acylimino group to the imidazole ring.<sup>122</sup> Pyridine *N*-acylimines exchange at the 2-, 4-, and 6-positions only in the presence of bases.<sup>8</sup>

## IV. Chemical Properties

Heteroaromatic *N*-imines and *N*-aminoazonium salts show a variety of reactivities, depending on the nature of the heteroaromatic ring and the substituents on the imino or amino nitrogen. The most important types of the reactions are (i) reactions with electrophiles at the imino or amino nitrogen, (ii) reactions with nucleophiles on the heteroaromatic ring, (iii) 1,3-dipolar cycloaddition, (iv) 6 $\pi$ -electrocyclic reaction of 1,5-dipoles (mainly thermal reaction), (v) 4 $\pi$ -electrocyclic reaction (mainly photochemical reaction), and (vi) N—N bond cleavage (by thermolysis, photolysis, oxidation, and reduction).

<sup>138</sup> T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.* **14**, 506 (1966).

<sup>139</sup> H. G. O. Becker, D. Nagel, and H.-J. Timpe, *J. Prakt. Chem.* [2] **315**, 97 (1973).

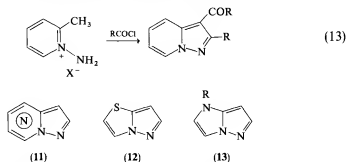
## A. REACTIONS WITH ELECTROPHILES

## 1. Alkylation and Acylation

As already described (Section II,A,1), reaction of the *N'*-unsubstituted *N*-imines and *N*-aminoazonium salts with acylating agents, imidoyl chloride, and active halobenzenes provides a general method for the preparation of the *N'*-substituted derivatives.

In general, alkylation and acylation of the *N*-acylimines take place at the imino nitrogen, although two reactive sites, the carbonyl oxygen and imino nitrogen, are available.<sup>13-15,45,48,79,140</sup> By contrast, alkylation of *N*-imidoylimines and *N*-vinylimines occurs at the imidoyl nitrogen and vinyl carbon, respectively.<sup>140</sup>

Treatment of 2-alkyl- or 2-hydroxymethyl-1-aminopyridinium salts with acyl or aroyl chlorides in the presence of base causes cyclization to pyrazolo[1,5-*a*]pyridine derivatives. If the 3-position is unsubstituted, acylation occurs at this position under the reaction conditions (Eq. 13).<sup>18,141</sup> There is good evidence that the initial step is acylation of the *N*-amino group. This reaction has been extended to the synthesis of various bridgehead nitrogen heterocyclic systems including pyrazolodiazines (11),<sup>9</sup> pyrazolo[5,1-*b*]thiazole (12),<sup>142</sup> and imidazo[1,2-*b*]pyrazole (13).<sup>142</sup>



1,2-Diaminopyridinium salts also cyclize with acylating agents to give *s*-triazolo[1,5-*a*]pyridines (Eq. 14).<sup>138,143</sup> Applications of this reaction to aminodiazines,<sup>144</sup> 2-aminothiazoles,<sup>145,146</sup> 2-amino-1,3,4-thiadiazole,<sup>147</sup>

<sup>140</sup> A. Kakehi, S. Ito, K. Uchiyama, and K. Kondo, *J. Org. Chem.* **43**, 2896 (1978).

<sup>141</sup> S. Suzue, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **21**, 2146 (1973).

<sup>142</sup> H. Koga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 482 (1974).

<sup>143</sup> K. T. Potts, H. R. Burton, and J. Bhattacharyya, *J. Org. Chem.* **31**, 260 (1966).

<sup>144</sup> Y. Tamura, J.-H. Kim, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 107 (1975).

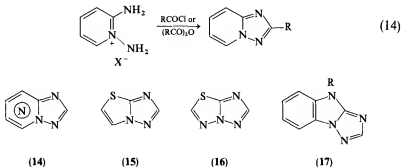
<sup>145</sup> Y. Tamura, H. Hayashi, J.-H. Kim, and M. Ikeda, *J. Heterocycl. Chem.* **10**, 947 (1973).

<sup>146</sup> Y. Tamura, H. Hayashi, E. Saeiki, J.-H. Kim, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 459 (1974).

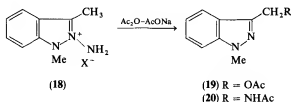
<sup>147</sup> Y. Tamura, H. Hayashi, J.-H. Kim, and M. Ikeda, *Chem. Pharm. Bull.* **27**, 2521 (1979).



and 2-amino-1-methylbenzimidazole<sup>147</sup> give the corresponding fused s-triazole derivatives (14–17).



Attempted cyclization of 2-amino-1,3-dimethylindazolium salt (18) with a large excess of acetic anhydride in the presence of sodium acetate gives instead the rearranged products 19 and 20 along with the deaminated product.<sup>36</sup> A similar rearrangement occurs with 2-amino-1,3,5-trimethylpyrazolium salt, which gives 5-acetoxymethyl-1,3-dimethylpyrazole.<sup>36</sup> This type of rearrangement is well known in the heteroaromatic *N*-oxides.

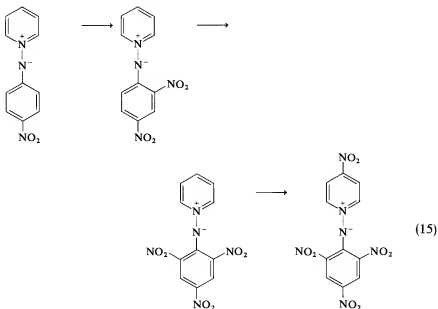


## 2. Nitration

Brief heating of pyridine *N*-(*o*- or *p*-nitrophenyl)imines in a mixture of nitric acid and concentrated sulfuric acid (1:1) gives the same 2,4-dinitrophenyl derivative. Further reaction gives the 2,4,6-trinitrophenyl derivative and, finally, 4-nitropyridine *N*-(trinitrophenyl)imine (Eq. 15). The nitration at the 4-position of the pyridine ring may reflect the high electron density on that position by a back-donating effect of the negative charge.<sup>148</sup>

Nitration of pyridine *N*-benzenesulfonylimine and *N*-benzoylimine in acetic acid–acetic anhydride takes place at the imino nitrogen to give the

<sup>148</sup> T. Okamoto, S. Hayashi, H. Horikiri, and M. Hirobe, *Yakugaku Zasshi* **91**, 261 (1971) [*CA* **74**, 99819 (1971)].



*N*-nitroimine.<sup>8</sup> 1-Alkyl-1,2,4-triazole 4-acylimines and 4-sulfonylimines behave similarly.<sup>124</sup> The *N*-nitroimines are also formed by nitration of the *N*-aminoazonium salts in acetic acid–anhydride or trifluoroacetic acid–anhydride mixtures or by treatment with nitronium tetrafluoroborate (Section II,A,1).<sup>61,114,123</sup>

### 3. Reaction with Nitrous Acid

*N*-Aminoazonium salts and *N*-imines are deaminated by nitrous acid to give the parent heterocycles.<sup>44,149</sup>

### 4. Reaction with Diazonium Salts

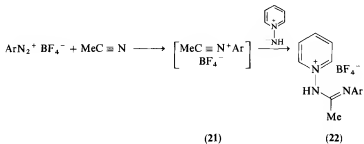
*N*-Aminopyridinium chloride and pyridine *N*-imine react with aryl diazonium salts to give aryl azides in high yields.<sup>149,150</sup>

Interestingly, when *N*-aminopyridinium tetrafluoroborate is treated with aryl diazonium tetrafluoroborates (bearing electron-withdrawing groups in

<sup>149</sup> T. Okamoto and S. Hayashi, *Yakugaku Zasshi* **86**, 766 (1966) [*CA* **65**, 20116 (1966)].

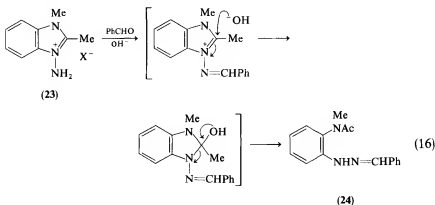
<sup>150</sup> R. A. Abramovitch, M. N. Inbasekaran, S. Kato, and G. M. Singer, *J. Org. Chem.* **41**, 1717 (1976).

the aryl group) in acetonitrile, *N*-(arylacetimido)l aminopyridinium salts **22** are formed. It is suggested that the nitrilium ion **21** resulting from the *N*-arylation of solvent acetonitrile is attacked by the *N*-aminopyridinium salt, giving **22**.<sup>150</sup>



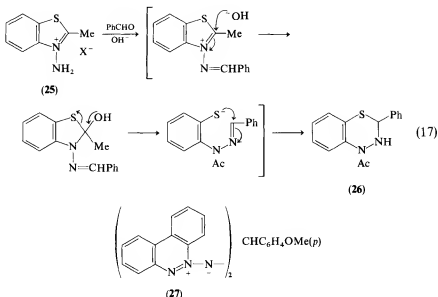
### 5. Reaction with Carbonyl Compounds

Early reports indicate that *N*-aminopyridinium salts react with aromatic aldehydes in the presence of base to give nitriles as the major products.<sup>1</sup> Completely different reaction courses emerge when the 1-methyl-3-amino-benzimidazolium salt **23** and 2-methyl-3-aminobenzothiazolium salt **25** are allowed to react with benzaldehyde under the similar conditions, affording a benzaldehyde phenylhydrazone **24**<sup>151</sup> and a 2,3-dihydro-1,3,4-benzothiadiazine **26**,<sup>152</sup> respectively; likely reaction pathways are suggested in Eqs. (16) and (17). Benzo[*c*]cinnoline *N*-imine reacts with *p*-anisaldehyde to give the bis-*N*-imine **27**.<sup>44</sup>



<sup>151</sup> Y. Tamura, H. Hayashi, Y. Nishimura, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 225 (1975).

<sup>152</sup> Y. Tamura, H. Hayashi, and M. Ikeda, *Synthesis*, 126 (1974).



The reaction of *N*-aminoazonium salts with aliphatic and aromatic aldehydes in the absence of base gives the Schiff base type compounds **28**.<sup>151,153-156</sup> Some aliphatic ketones also react with *N*-aminoazonium salts.<sup>40,155</sup> Hexane-2,5-dione reacts with *N*-aminopyridinium perchlorate to give 1-(1'-pyrrolyl)pyridinium cation **29** together with some of the bisperchlorate **30**.<sup>157</sup> Certain esters such as diethyl malonate and ethyl cyanoacetate react with *N*-aminopyridinium salts in the presence of base to give the corresponding *N*-acylimines **31**.<sup>48</sup> However, the reaction of ethyl acetoacetate and acetylacetone with *N*-aminoazonium salts in the presence of base gives 1,3-dipolar cycloaddition products (Section IV,C,1).<sup>36,154,158</sup> The reaction of ethyl acetoacetate with 1-alkyl-1,2,4-triazole 4-imine affords zwitterionic triazolo[4,3-*b*]pyridazines **32**.<sup>139,159</sup>

<sup>153</sup> T. Okamoto, M. Hirobe, and R. Sato, *Yakugaku Zasshi* **87**, 994 (1967) [*CA* **68**, 12822 (1968)].

<sup>154</sup> K. T. Potts, R. Dugas, and C. R. Surapaneni, *J. Heterocycl. Chem.* **10**, 821 (1973).

<sup>155</sup> T. V. Troepf'skaya and Yu. P. Kitaev, *Khim. Geterotsikl. Soedin.*, 1219 (1973) [*CA* **80**, 14174 (1974)].

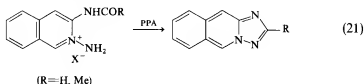
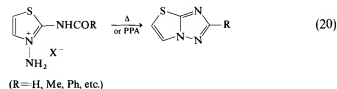
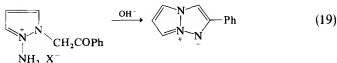
<sup>156</sup> A. R. Katritzky, J. Banerji, A. Boonyarakvanich, A. T. Cutler, N. Dennis, S. Q. A. Rizvi, G. J. Sabongi, and H. Wilde, *J. C. S. Perkin I*, 399 (1979).

<sup>157</sup> A. R. Katritzky and J. W. Suwinski, *Tetrahedron* **31**, 1549 (1975).

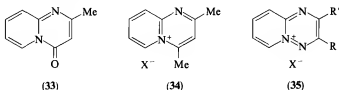
<sup>158</sup> Y. Tamura, A. Yamakami, and M. Ikeda, *Yakugaku Zasshi* **91**, 1154 (1972) [*CA* **76**, 34164 (1972)].

<sup>159</sup> H.-J. Timpe, H. G. O. Becker, and R. Radeglia, *J. Prakt. Chem.* [2] **319**, 945 (1977).





1,2-Diaminopyridinium iodide undergoes reaction with ethyl acetate and acetylacetone to form somewhat unexpected products, the pyrido[1,2-*a*]pyrimidine derivatives **33** and **34**, respectively.<sup>154</sup> The initial step has been shown to be decomposition of 1,2-diaminopyridinium iodide to 2-aminopyridinium iodide which undergoes condensation with  $\beta$ -dicarbonyl compounds. The reaction of 1,2-diaminopyridinium salt with 1,2-dicarbonyl compounds gives pyrido[1,2-*b*][1,2,4]-triazinium salts **35**.<sup>161</sup>



## 6. Reaction with 2H-Azirines

Reaction of pyridine *N*-imines with 2*H*-azirines gives pyrido[1,2-*b*]triazine derivatives **38**.<sup>162,163</sup> Substituted pyridine, quinoline, and isoquinoline *N*-imines react in an analogous manner. Although, in principle, two modes of cycloaddition are feasible with 3-substituted pyridine *N*-imines, the reaction of the 3-methyl derivative involves cycloaddition at the more hindered site.

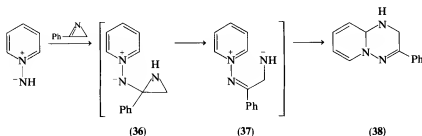
<sup>161</sup> N. V. Baranova, A. K. Sheinkman, and A. N. Kost, *Khim. Geterotsikl. Soedin.*, 1266 (1973) [*CA* **80**, 3473 (1974)].

<sup>162</sup> A. Kakehi, S. Ito, and T. Manabe, *J. Org. Chem.* **40**, 544 (1975).

<sup>163</sup> A. Kakehi, S. Ito, T. Manabe, H. Amano, and Y. Shimaoka, *J. Org. Chem.* **41**, 2739 (1976).

On the other hand, the reaction of pyridine *N*-imines bearing an electron-withdrawing group (CN and CO<sub>2</sub>Me) at the 3-position gives exclusively inverse orientation to the less hindered position, which is in contrast to the course of the 1,3-dipolar cycloaddition of the same pyridine *N*-imines with ethyl propiolate (Section IV,C,1).

The foregoing reaction is probably initiated by nucleophilic addition of the *N*-imines to the 2*H*-azirines to form **36** which may undergo homo-1,5-dipolar cyclization or ring opening followed by cyclization of 1,6-dipoles **37**. This novel heterocyclic system was first prepared by the reaction of pyridine *N*-imines with  $\alpha$ -chlorocinnamates, in which azirine intermediates were postulated.<sup>164</sup> As a variation, use of azirine intermediates generated *in situ* from acetophenone oxime *O*-tosylate or dimethylhydrazine methiodide under the Neber reaction conditions also produces the pyrido[1,2-*b*]triazines **38**.<sup>163,165</sup>



### 7. Reaction with Cyclopropenones

Diphenylcyclopropenone and its thione are well known as highly electrophilic carbonyl compounds, which react with pyridine *N*-acylimines to give 1,3-oxazin-6-ones **39**,<sup>46,166</sup> and -6-thiones,<sup>46</sup> respectively. The reaction of pyridine *N*-imine with the cyclopropenone in methanol gives methyl 3-aminoacrylate **40**.<sup>167</sup> It is likely that these reactions involve ketene intermediates which are intercepted either by internal nucleophiles or by the solvent. Benzo[*c*]cinnoline *N*-acylimines also give the oxazinones **39**, whereas the *N*-benzimidoylimines give stable 1:1 adducts as a result of a difference in the preferred site of attack by the electrophilic cyclopropenone (Eq. 22).<sup>168</sup>

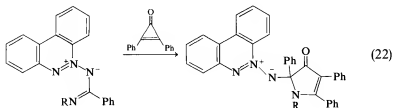
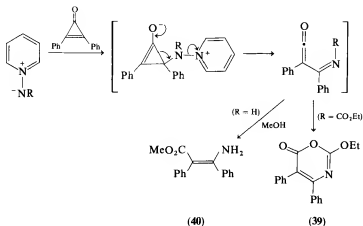
<sup>164</sup> A. Kakehi and S. Ito, *J. Org. Chem.* **39**, 1542 (1974).

<sup>165</sup> A. Kakehi, S. Ito, T. Manabe, T. Maeda, and K. Imai, *J. Org. Chem.* **42**, 2514 (1977).

<sup>166</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.* **36**, 2451 (1971).

<sup>167</sup> A. Kascheres and D. Marchi, *J. Org. Chem.* **40**, 2985 (1975).

<sup>168</sup> J. J. Barr, R. C. Storr, and V. K. Tandon, *J. C. S. Perkin I*, 1147 (1980).



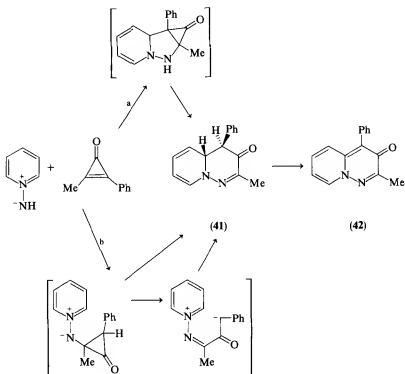
Another interesting difference in reactivity has been observed when pyridine *N*-imine is allowed to react with methylphenylcyclopropanone in methanol to give 3*H*-pyrido[1,2-*b*]pyridazin-3-one **42** in addition to ethyl 3-aminoacrylate.<sup>169,170</sup> If the reaction is carried out in aprotic solvent, **42** is formed in fairly good yield. In some cases, 4,4a-dihydro intermediates **41** are isolated. In principle, two isomeric pyridopyridazinones may be formed by the cycloaddition of 3-methylpyridine *N*-imine; however, the cycloaddition occurs predominantly at the sterically less hindered site. By comparison, the reactions of the same *N*-imine with 2*H*-azirines (Section IV,A,6) and with ethyl propiolate (Section IV,C,1) take place predominantly at the more hindered site.

Possible pathways to the pyridopyridazinones are shown in Scheme 3. One route (path a) involves initial 1,3-dipolar cycloaddition of the *N*-imine with the cyclopropanone and subsequent opening of the cyclopropanone ring with transfer of the amino hydrogen to afford **41**. An alternate route (path b) is very similar to that proposed for the reaction with 2*H*-azirines (Section IV,A,6).

<sup>169</sup> A. Kascheres and D. Marchi, *J. C. S. Chem. Commun.*, 275 (1976).

<sup>170</sup> A. Kascheres, D. Marchi, and J. A. R. Rodrigues, *J. Org. Chem.* **43**, 2892 (1978).





SCHEME 3

Reaction of 1,2-diaminopyridinium salt with diphenylcyclopropenone in ethanol in the presence of base gives ethyl 3-amino-2,3-diphenylacrylate, whereas the reaction in benzene gives 3-amino-*N*-(2-pyridyl)-2,3-diphenylacrylamide.<sup>171</sup>

### 8. Reaction with Cyclopropenium Ions

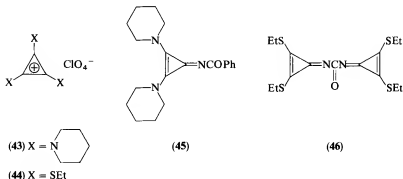
Pyridine *N*-acylimines react with the amino-substituted cyclopropenium ion **43** in DMSO at 80°C to give cyclopropene imines, e.g., **45**.<sup>172</sup> In contrast, the reaction with thio-substituted cyclopropenium ion **44** under the same conditions gives *N,N'*-dicyclopropenylidene urea derivative **46**.<sup>173</sup> Although the precise pathway involved in these reactions has not been established, the

<sup>171</sup> Y. Tamura, J.-H. Kim, Y. Sumida, and M. Ikeda, *Yakugaku Zasshi* **95**, 1497 (1975) [*CA* **84**, 90091 (1975)].

<sup>172</sup> S. Inoue, G. Yasuda, and T. Hori, *Chem. Lett.*, 1215 (1976).

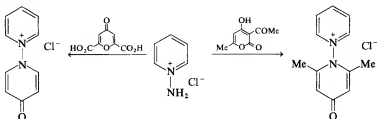
<sup>173</sup> S. Inoue, G. Yasuda, and T. Hori, *Bull. Chem. Soc. Jpn.* **51**, 3653 (1978).

initial step involves nucleophilic attack of the *N*-acylimine to the cyclopropenium ions.



### 9. Reaction with Pyrones

*N*-Aminopyridinium salts react with certain pyrones to give 1-pyridinio-4-pyridone cations.<sup>174,175</sup>



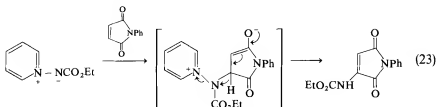
### 10. Michael-Type Addition to $\alpha,\beta$ -Unsaturated Carbonyl Compounds

In general, the reaction of heteroaromatic *N*-imines with  $\alpha,\beta$ -unsaturated carbonyl compounds gives cycloaddition products as described later (Section IV,C). However, in some cases they can act as nucleophiles. Thus, pyridine *N*-ethoxycarbonylimine, in the presence of silicic acid, reacts with fumarate, maleic anhydride, *N*-phenylmaleimide, *p*-benzoquinone, and  $\alpha$ -naphthoquinone to give the corresponding enamines in good yields (Eq. 23).<sup>176</sup> Pyridine *N*-imine also reacts with dimethyl maleate to give dimethyl aminofumarate.<sup>164</sup>

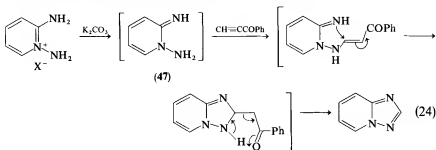
<sup>174</sup> A. R. Katritzky and M. P. Sammes, *J. C. S. Chem. Commun.*, 247 (1975).

<sup>175</sup> M. P. Sammes, H. K. Wah, and A. R. Katritzky, *J. C. S. Perkin I*, 327 (1977).

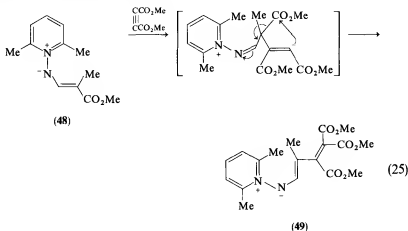
<sup>176</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron* **28**, 1469 (1972).



1,2-Diaminopyridinium salt reacts, in the presence of base, with a variety of  $\alpha,\beta$ -unsaturated compounds such as benzoylacetylenes, benzalacetophenone, ethoxymethylenepentane-2,4-dione, and diethyl ethoxymethylenemalonate to give *s*-triazolo[1,5-*a*]pyridine derivatives, presumably via 1-amino-2-imino-1,2-pyridine (**47**) (Eq. 24).<sup>171</sup> These reactions involve formal cleavage of the carbon-carbon double and triple bonds.



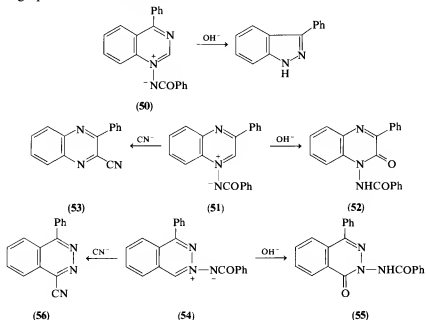
An interesting rearrangement is observed when pyridine *N*-vinylimine **48** is allowed to react with dimethyl acetylenedicarboxylate to give the *N*-dienylimine **49**.<sup>54</sup> The initial step in the reaction may involve nucleophilic attack of **48** to dimethyl acetylenedicarboxylate followed by intramolecular migration of an ester group (Eq. 25).



## B. REACTIONS WITH NUCLEOPHILES

## 1. Reaction with Alkali

Although pyridine or quinoline *N*-acylimines are relatively stable to alkali, quinazoline 1-benzoylimine **50** undergoes ring contraction to 3-phenylindazole, and quinoxaline 1-benzoylimine **51** and phthalazine 3-benzoylimine **54** afford **52** and **55**, respectively.<sup>177</sup> Alkaline treatment of 1-alkyl-1,2,4-triazole 4-acylimines gives a variety of products derived from the ring-opened intermediates.<sup>111</sup>



## 2. Reaction with Cyanide Ion

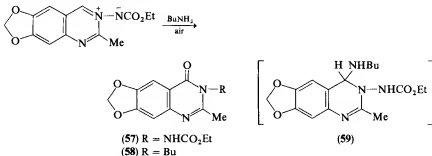
Pyridine *N*-imines react with cyanide ion to give *s*-triazolo[1,5-*a*]pyridine, obtained from 1,3-dipolar cycloaddition of initially formed 4-cyanopyridines with pyridine *N*-imines (Section IV.C.1).<sup>138</sup> Quinoline *N*-imine gives 4-cyanoquinoline, 2,4-dicyanoquinoline, 4-cyanoquinaldamide, and a 1,3-dipolar cycloaddition product, depending on the solvent used.<sup>14</sup>

In contrast to pyridine and quinoline *N*-acylimines which fail to react with cyanide ion, quinoxaline 1-benzoylimine **51** and phthalazine 3-benzoylimine **54** readily react with cyanide ion to give in high yields 2-cyano-3-phenylquinoxaline (**53**) and 1-cyano-4-phenylphthalazine (**56**), respectively.<sup>177</sup>

<sup>177</sup> Y. Tamura, Y. Miki, K. Nakamura, and M. Ikeda, *J. Heterocycl. Chem.* **13**, 23 (1976).

### 3. Reaction with Amines

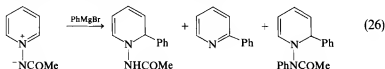
Refluxing quinazoline 3-acylimines (bearing no substituent attached at C-4) with butylamine under air gives two oxidation products, **57** and **58**.<sup>178</sup> This oxidation probably involves the intermediate **59**.



*N*-Amino-2-chloropyridinium salt reacts with hydroxylamine to give 1-amino-2-hydroxyimino-1,2-dihydropyridine.<sup>179</sup>

### 4. Reaction with Grignard Reagents

The reaction of pyridine *N*-acetylimines with phenylmagnesium bromide has been reported to give 2-phenyl-1,2-dihydropyridine derivatives as major products (Eq. 26).<sup>15</sup> The structure of the 1,2-dihydropyridines is mainly based on a comparison of their UV spectra with those of 1-hydroxy-2-phenyl-1,2-dihydropyridines. However, since the structures of the latter have recently been revised to 5-phenyl-2,4-pentadienyl oximes,<sup>180</sup> further evidence for the 1,2-dihydropyridine structure would be desirable.



### 5. Reaction with Hydroperoxides

Pyridine *N*-phenylimines react with hydroperoxides (*t*-butylhydroperoxide and hydrogen peroxide) to give 1,6-dihydropyridazines.<sup>181</sup> This

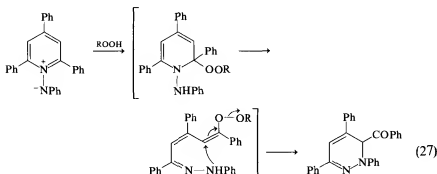
<sup>178</sup> J. Fetter, G. Barta-Szalai, A. Jaber, and E. Bertha, *Period. Polytech., Chem. Eng.* **22**, 143 (1978) [*CA* **89**, 215344 (1978)].

<sup>179</sup> A. Tomazic, M. Tisler, and B. Stanovnik, *Heterocycles* **12**, 1157 (1979).

<sup>180</sup> T. J. van Bergen and R. M. Kellogg, *J. Org. Chem.* **36**, 1705 (1971).

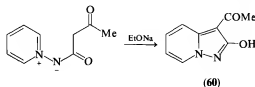
<sup>181</sup> V. Snieckus and G. Kan, *Tetrahedron Lett.*, 2267 (1970).

reaction may involve nucleophilic attack by hydroperoxide ion at the 2-position of the pyridine *N*-imines followed by breakdown of the intermediate (Eq. 27).



### 6. Intramolecular Carbanionic Cyclization

An intramolecular cyclization occurs upon treatment of pyridine *N*-acetoacetylamine with sodium ethoxide to give pyrazolo[1,5-*a*]pyridine **60**.<sup>47</sup>



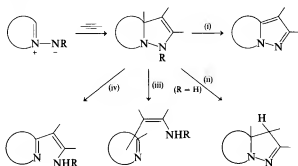
### C. 1,3-DIPOLAR CYCLOADDITIONS

Since Huisgen *et al.* first demonstrated the 1,3-dipolar character of pyridine *N*-imine in 1962,<sup>182</sup> the 1,3-dipolar cycloaddition reactions of the heteroaromatic *N*-imines have been explored extensively. The reactivity stems from the azomethine structure of the *N*-imines.<sup>183</sup> The cycloaddition of a variety of activated alkynes and alkenes to the *N*-imines yields fused dihydropyrazoles and tetrahydropyrazoles, respectively. However, the aromaticity of the heteroaromatic ring is destroyed at this stage, so that such primary cycloadducts usually undergo further reaction to achieve stabilization in various ways as shown in Scheme 4: (i) aromatization, (ii) hydrogen transfer, (iii) rearomatization by rearrangement, and (iv) rearomatization by N—N

<sup>182</sup> R. Huisgen, R. Grashey, and R. Krishke, *Tetrahedron Lett.*, 387 (1962).

<sup>183</sup> R. Huisgen, *Angew. Chem., Int. Edit. Engl.* **2**, 565 (1963).

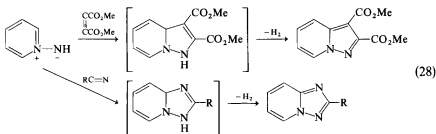
bond cleavage. These secondary reaction courses are highly dependent upon the nature of the heteroaromatic ring and the substituents (in particular on the imino nitrogen).



SCHEME 4

### 1. Six-Membered Heteroaromatic N-Imines

The 1,3-dipolar cycloaddition of pyridine *N'*-unsubstituted *N*-imines with activated dipolarophiles such as acetylenic esters,<sup>58,120,182,184</sup> ketones,<sup>185</sup> and nitriles,<sup>186</sup> ethyl acetoacetate,<sup>154,159</sup> acetylacetone (Section IV.A.6.),<sup>154</sup>  $\beta$ -haloacrylates,<sup>54,159</sup> and nitriles<sup>138</sup> provides particularly facile entries to many pyrazolo[1,5-*a*]pyridines and triazolo[1,5-*a*]pyridines (Eq. 28).



Since the *N*-imines are generally unstable, the reaction is usually carried out by treating the *N*-aminoazonium salts with base in the presence of 1,3-dipolarophiles. The versatility of this reaction is demonstrated by application to a wide range of the six-membered heteroaromatic *N*-imines which include substituted pyridine *N*-imines,<sup>187</sup> di-*N*-imines of 2,2'-bipyridyl and

<sup>184</sup> V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.* **33**, 2062 (1968).

<sup>185</sup> K. T. Potts, H. P. Youzwak, and S. J. Zurawel, *J. Org. Chem.* **45**, 90 (1980).

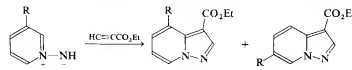
<sup>186</sup> T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C*, 481 (1970).

<sup>187</sup> Y. Tamura, Y. Sumida, Y. Miki, and M. Ikeda, *J. C. S. Perkin I*, 406 (1975).

4,4'-bipyridyls,<sup>126</sup> diazine *N*-imines,<sup>9,188,189</sup> benzodiazine *N*-imines,<sup>190</sup> naphthyridine *N*-imines,<sup>190</sup> quinoline *N*-imine,<sup>17</sup> isoquinoline *N*-imine,<sup>17,190</sup> and phenanthridine *N*-imine.<sup>17,33</sup>

The effect of 3-substituents upon orientation in the reaction between a series of 3-substituted pyridine *N*-imines and ethyl propiolate has been investigated.<sup>187</sup> The results indicate that (i) unless a large substituent is present at the 3-position, the cycloaddition occurs preferentially at C-2 of the pyridine ring, regardless of the electron-donating or electron-withdrawing character of the substituent; (ii) steric hindrance by a 3-substituent to attack at C-2 becomes important with the larger 3-substituents; and (iii) the 3-hydroxy-, 3-amino-, and 3-acetamidopyridine *N*-imines produce exclusively 4-substituted pyrazolo[1,5-*a*]pyridines. The observed regioselectivity is rationalized in terms of electronic and steric factors and of hydrogen-bond formation (see Table I).

TABLE I  
FORMATION OF ETHYL PYRAZOLO[1,5-*a*]PYRIDINE-3-CARBOXYLATES



R	4-Isomer	6-Isomer
Me	68 <sup>a</sup> (25) <sup>b</sup>	32(16)
Et	70(23)	30(11)
CH <sub>2</sub> Ph	63(31)	37(15)
OH	100(8) <sup>c</sup>	0
NH <sub>2</sub>	100(8)	0
NHAc	100(14)	0
NMeAc	73(20)	27(13)
Cl	64(6)	36(10)
Br	49(13)	51(16)
I	44(11)	56(14)
CN	73(17)	27(9)
CO <sub>2</sub> Et	65(31)	35(11)
CONEt <sub>2</sub>	36(17)	64(46)

<sup>a</sup> Product ratio determined by GLC analyses

<sup>b</sup> Isolated yield (%).

<sup>c</sup> Accompanied by a trace of an unidentified product.

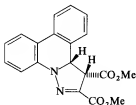
<sup>188</sup> C. W. Rees, R. W. Stephenson, and R. C. Storr, *J. C. S. Chem. Commun.*, 941 (1974).

<sup>189</sup> Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* **19**, 2106 (1971).

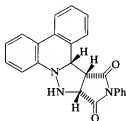
<sup>190</sup> Y. Tamura, Y. Miki, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 119 (1975).



In some cases nonaromatized adducts are isolated. The reaction of isoquinoline *N*-imine<sup>17,190</sup> and phenanthridine *N*-imine<sup>17,33</sup> with dimethyl acetylenedicarboxylate gives tautomeric isomers of the primary adducts, e.g., **61**. These *N*-imines also react with *N*-phenylmaleimide to give the primary 1:1 cycloadducts, e.g., **62**.<sup>33,190</sup> Of particular interest is the reaction of isoquinoline *N*-imine with mesityl oxide which produces **63**. This reaction involves disproportionation and elimination of methane from the primary adduct.<sup>17</sup>



(61)

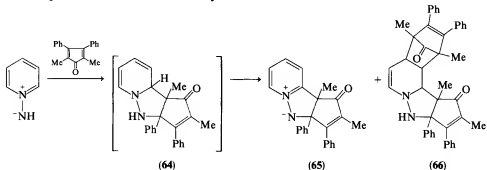


(62)



(63)

Very recently it has been reported that pyridine *N*-imine reacts with a cyclopentadienone to give a new ylide **65** and a 1:2 adduct **66**.<sup>191</sup> The formation of **65** and **66** can be rationalized in terms of the intermediacy of a primary adduct **64** which is either dehydrogenated to **65** or intercepted by the cyclopentadienone to give **66**. Such an intermediate was isolated from the reaction of quinoline *N*-imine and tetracyclone.



(64)

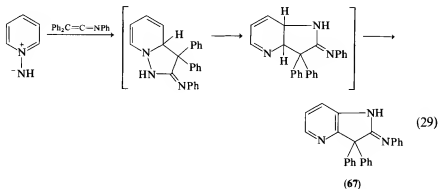
(65)

(66)

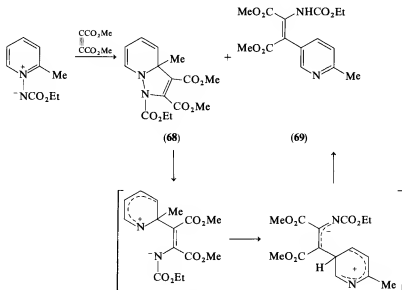
An interesting rearrangement has been observed in the reaction of pyridine *N*-imines with triarylketeneimines: an initial 1,3-dipolar cycloaddition is followed by a [1,5]-sigmatropic rearrangement with the subsequent loss of hydrogens, leading to the formation of 1*H*-pyrrolo[3,2-*b*]pyridines **67** (Eq. 29).<sup>192</sup>

<sup>191</sup> Y. Yamashita and M. Masumura, *Tetrahedron Lett.*, 1765 (1979).

<sup>192</sup> M. W. Barker and W. E. McHenry, *J. Org. Chem.* **44**, 1175 (1979).



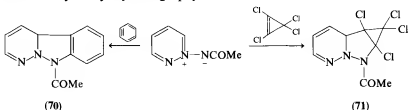
The *N*-acylimines also undergo 1,3-dipolar cycloadditions with various 1,3-dipolarophiles. The variation in reactivity is in the order *N*-alkoxycarbonylimine > *N*-acetylimine > *N*-benzoylimine, the differences being attributed to variations in electron density about the imino nitrogen, being greater for the *N*-alkoxycarbonylimines than for the *N*-benzoylimines. The primary cycloadducts have been isolated in many cases. The reaction of 2-methylpyridine *N*-ethoxycarbonylimine with dimethyl acetylenedicarboxylate gives the primary addition product **68**, which is spontaneously transformed into **69**.<sup>67</sup> One of the possible mechanistic explanations for the rearrangement is depicted in Scheme 5. A similar rearrangement has been



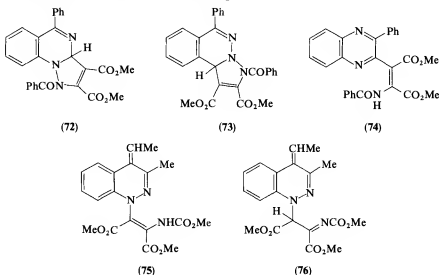
SCHEME 5

observed in the reaction of 2-methylpyridine *N*-benzoylimine<sup>193</sup> and 2,6-dimethylpyridine *N*-(methoxycarbonyl-ethenyl)imine<sup>54,56</sup> with acetylenic esters.

Pyridazine *N*-acetylimine reacts with benzyne to give 1:1 cycloadduct **70**, which has been shown to be a precursor of a variety of heterocyclic compounds.<sup>194</sup> The same *N*-imine undergoes 1,3-dipolar cycloaddition with perhalocyclopropanes to give tricyclic adducts **71**,<sup>195</sup> the structure being established by X-ray crystallography.



1,3-Dipolar cycloaddition of 4-phenylquinazoline 1-benzoylimine (**50**) and 1-phenylphthalazine 3-benzoylimines (**54**) with dimethyl acetylenedicarboxylate gives primary 1:1 cycloadducts **72** and **73**, whereas 3-phenylquinoxaline 1-benzoylimine (**51**) affords a product **74** which is formed by ring opening of a primary adduct.<sup>177</sup> 4-Ethyl-3-methylcinnoline 1-ethoxycarbonylimine also gives ring-opened products **75** and **76**.<sup>188</sup>

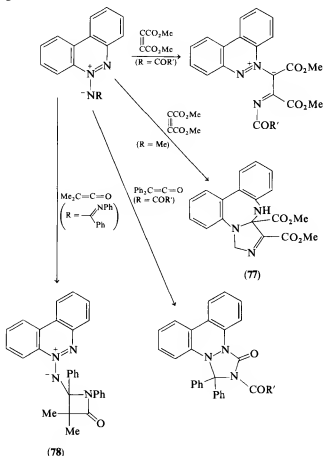


<sup>193</sup> T. Sasaki, K. Kanematsu, A. Kakchi, and G. Ito, *Bull. Chem. Soc. Jpn.* **45**, 2050 (1972).

<sup>194</sup> H. Igeta, H. Arai, H. Hasegawa, and T. Tsuchiya, *Chem. Pharm. Bull.* **23**, 2791 (1975).

<sup>195</sup> A. Ohsawa, I. Wada, H. Igeta, T. Akimoto, A. Tsuji, and Y. Iitaka, *Tetrahedron Lett.*, 4121 (1978).

Benzo[*c*]cinnoline *N*-acylimines and *N*-alkylimines show interesting reactivities toward dimethyl acetylenedicarboxylate and some ketenes as summarized in Scheme 6.<sup>196-199</sup> A multistep mechanism for the formation of **77** has been proposed. In contrast, the *N*-(*N*-phenylbenzimidoyl)imines undergo [2 + 2]-cycloaddition with ketenes to the C=N bond to give  $\beta$ -lactams, e.g., **78**.<sup>200,201</sup>



SCHEME 6

<sup>196</sup> S. F. Gait, M. J. Rance, C. W. Rees, and R. C. Storr, *J. C. S. Chem. Commun.*, 688 (1972).

<sup>197</sup> S. R. Challand, C. W. Rees, and R. C. Storr, *J. C. S. Chem. Commun.*, 837 (1973).

<sup>198</sup> S. R. Challand, S. F. Gait, M. J. Rance, C. W. Rees, and R. C. Storr, *J. C. S. Perkin I*, 26 (1975).

<sup>199</sup> M. J. Rance, C. W. Rees, P. Spagnolo, and R. C. Storr, *J. C. S. Chem. Commun.*, 658 (1974).

<sup>200</sup> S. H. Alsop, J. J. Barr, R. C. Storr, A. F. Cameron, and A. A. Freer, *J. C. S. Chem. Commun.*, 888 (1976).

<sup>201</sup> J. J. Barr and R. C. Storr, *J. C. S. Perkin I*, 192 (1979).

The stereochemistry of the 1,3-dipolar cycloaddition of the heteroaromatic *N*-imines has been investigated in some detail by using the reaction of phenanthridine *N*-benzoylimine with a series of activated olefins such as *N*-methylmaleimide, maleic anhydride, diethyl maleate, methyl acrylate, methyl methacrylate, and methyl *trans*-crotonate (e.g., Eq. 30).<sup>202</sup> The adducts from the former three have the all-*cis* stereochemistry. These results are rationalized in terms of secondary molecular orbital interactions. With acrylates such stereospecificity is lost, suggesting that this effect is of lesser importance in these cases (see Table II).

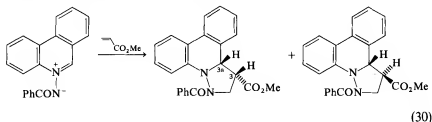


TABLE II  
PRODUCT DISTRIBUTION IN CYCLOADDITION REACTIONS OF  
PHENANTHRIDINE *N*-BENZOYLIMINE WITH OLEFINS

Olefin	<i>cis</i> (3H,3aH)-Adduct	<i>trans</i> (3H,3aH)-Adduct
<i>N</i> -Methylmaleimide	100(70) <sup>a</sup>	0(0)
Maleic anhydride	100(70)	0(0)
Dimethyl maleate	100(63)	0(0)
Methyl acrylate	52.4 <sup>a</sup> (60)	47.6(30)
Methyl methacrylate	55.9 <sup>a</sup> (40)	44.1(31)
Methyl <i>trans</i> -crotonate	~0(0)	~100(80)

<sup>a</sup> Product ratio determined by NMR spectroscopy.

<sup>b</sup> Isolated yield (%) in parentheses.

## 2. Five-Membered Heteroaromatic *N*-Imines

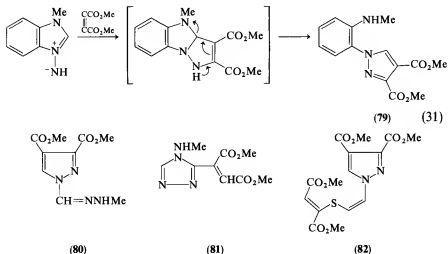
1,3-Dipolar cycloaddition of 1-alkylbenzimidazole *N*-imines with dimethyl acetylenedicarboxylate results in the formation of the ring-opened pyrazole derivative **79** (Eq. 31).<sup>151,203</sup> 1-Methyl-1,2,4-triazole 4-imine also reacts in a similar manner to give a pyrazole derivative (**80**),<sup>204</sup> but Summers and Elguero obtained a rather unusual product (**81**) from the same reac-

<sup>202</sup> Y. Tamura, Y. Miki, and M. Ikeda, *J. C. S. Perkin I*, 1702 (1976).

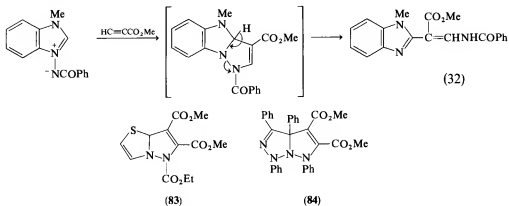
<sup>203</sup> Y. Tamura, H. Hayashi, J. Minamikawa, and M. Ikeda, *Chem. Ind. (London)*, 952 (1973).

<sup>204</sup> Y. Tamura, H. Hayashi, and M. Ikeda, *Chem. Pharm. Bull.* **24**, 2568 (1976).

tion.<sup>205</sup> In the reaction of thiazole *N*-imine the initially formed product further reacts with dimethyl acetylenedicarboxylate to give ultimately **82**.<sup>143,206</sup>



By contrast, the reactions of 1-methylbenzimidazole 3-acylimines<sup>207</sup> and 1-methyl-1,2,4-triazole 4-acylimines<sup>204</sup> with activated alkynes and alkenes result in the N—N bond cleavage of the primary adducts to regenerate benzimidazole and triazole ring systems (Eq. 32). Apparently, the driving force for these ring-opening reactions is derived from the relief of the strain in the 5/5 fused ring system.



<sup>205</sup> A. J. H. Summers and J. Elguero, *Bull. Soc. Chim. Fr.*, 3974 (1972).

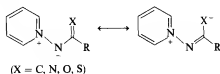
<sup>206</sup> K. T. Potts and D. R. Choudhury, *J. Org. Chem.* **42**, 1648 (1977).

<sup>207</sup> Y. Tamura, H. Hayashi, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 819 (1975).

Interestingly, the reaction of thiazole *N*-ethoxycarbonylimine with dimethyl acetylenedicarboxylate furnishes the primary 1:1 cycloadduct **83**.<sup>142</sup> 2-Phenyl-1,2,3-triazole 1-phenylimine also reacts with a variety of olefinic and acetylenic dipolarophiles to give 1:1 cycloadducts, e.g., **84**.<sup>95-97</sup>

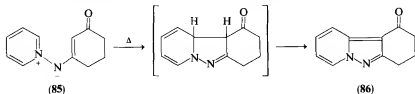
#### D. THERMAL REACTIONS

The most important and general types of reaction that occur when an *N'*-substituted *N*-imine is heated are (i) a  $6\pi$ -electrocyclic reaction of "1,5-dipoles"<sup>208</sup> (intramolecular 1,5-cyclization) and (ii) N—N bond fission. The reaction courses are highly dependent upon the nature of the substituent on the imino nitrogen.



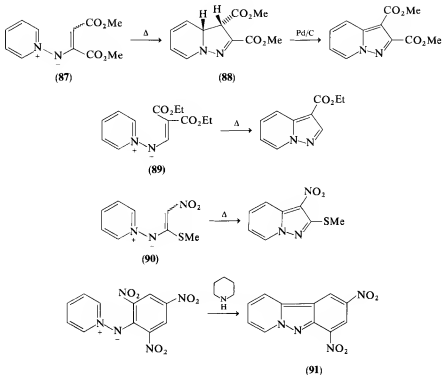
##### 1. *N*-Vinyl- and *N*-Arylimines

The first example of the intramolecular 1,5-cyclization has been shown with cyclic  $\beta$ -ketovinylimine **85**.<sup>51,52</sup> Refluxing **85** in toluene gives directly fully aromatized pyrazolo[1,5-*a*]pyridine **86**. As in this case, the cyclization is usually accompanied by aromatization. However, it is possible to isolate a dihydro intermediate in some instances. Thus, when left in chloroform at room temperature, **87** undergoes cyclization to give **88**, which can be dehydrogenated by palladium carbon to the aromatic compound.<sup>53</sup> Further examples of the cyclization are provided by the conversion of **89**<sup>55</sup> and **90**<sup>57,209</sup> into the corresponding pyrazolo[1,5-*a*]pyridines. Pyridine *N*-picrylimine yields a cyclization product **91** in the presence of piperidine, the key step being probably the electrocyclic reaction.<sup>74</sup>

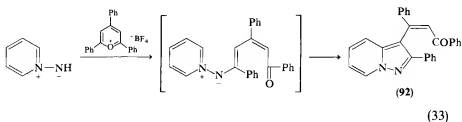


<sup>208</sup> H. Reimlinger, *Chem. Ber.* **103**, 1900 (1970).

<sup>209</sup> H. Fujito, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi* **97**, 1316 (1977) [*CA* **87**, 53048 (1977)].



Pyridine *N*-imine reacts with a pyrylium salt at room temperature, giving pyrazolo[1,5-*a*]pyridine **92**.<sup>210</sup> It is suggested that this reaction involves an unisolable *N*-vinylimine intermediate which undergoes cyclization followed by aromatization (Eq. 33).

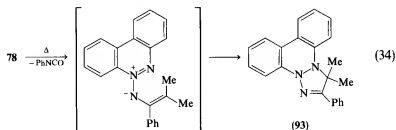


The 1,5-cyclization may also be involved in the formation of **93** by thermolysis of **78** (Eq. 34).<sup>201,211</sup>

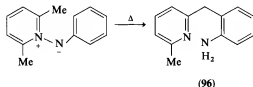
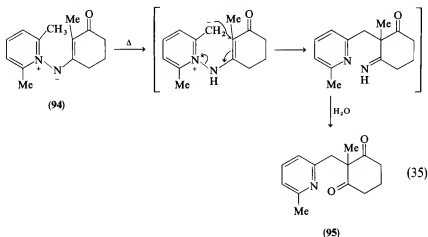
<sup>210</sup> T. Toda, H. Morino, Y. Suzuki, and T. Mukai, *Chem. Lett.*, 155 (1977).

<sup>211</sup> J. J. Barr and R. C. Storr, *J. C. S. Chem. Commun.*, 778 (1975).





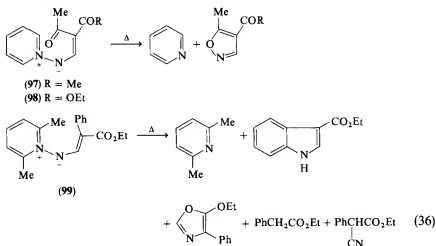
Some *N*-vinylimines take different reaction courses. For example, when *N*-vinylimine **94** is heated, a rearrangement takes place to give **95** (Eq. 35).<sup>51,52</sup> This reaction is closely related to a classical example of the rearrangement of 2,6-dimethylpyridine *N*-phenylimine to **96**.<sup>212</sup>



Conjugatively stabilized *N*-vinylimines such as **97** and **98** are thermally labile and, upon heating in benzene, undergo an intramolecular displacement of pyridine to give isoxazole derivatives in high yields.<sup>55</sup> Thermolysis of sterically hindered 2,6-dimethylpyridine *N*-vinylimine **99** affords many

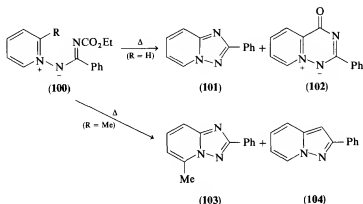
<sup>212</sup> K. Dimroth, G. Arnoldy, S. von Eicken, and G. Schiffler, *Justus Liebigs Ann. Chem.* **604**, 221 (1957).

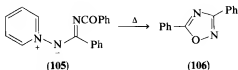
products as shown in Eq. (36).<sup>56</sup> A simple N—N bond fission is observed in thermolysis of pyridine *N*-(*p*-nitrophenyl)imine, giving pyridine and *p*-nitroaniline.<sup>62</sup>



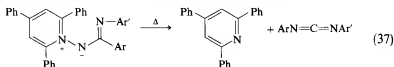
## 2. *N*-Imidoylimines

Thermal behavior of a variety of pyridine *N*-imidoylimines has been studied. Thermolysis of **100** in refluxing xylene gives 1,5-cyclization product **101**, together with six-membered betaine **102**. The 2-methylpyridine congener gives pyrazolo[1,5-*a*]pyridine **104** in addition to **103**.<sup>59,60</sup> By contrast *N*-imine **105** undergoes an intramolecular displacement to give a heterocyclic product **106**.<sup>59,60</sup>

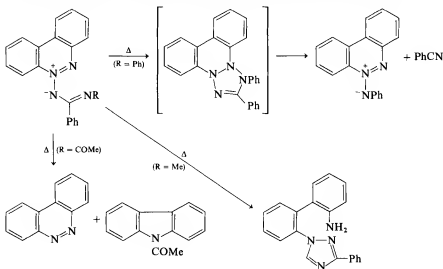




Thermolysis of 2,4,6-triphenylpyridine *N*-imidoylimines gives *N,N'*-diarylcarbodiimides in high yields (Eq. 37)<sup>89,90</sup>; it provides a useful synthetic entry to symmetrical and unsymmetrical diarylcarbodiimides.



A further example of the fact that minor changes in substituents lead to completely different reaction pathways is illustrated in Scheme 7.<sup>213,214</sup>



SCHEME 7

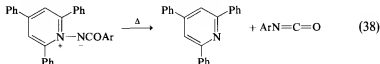
### 3. *N*-Acylimines

In spite of the fact that the *N*-acylimines exhibit 1,5-dipolar character, no intramolecular cyclization has been observed. The N—N bond cleavage

<sup>213</sup> J. J. Barr, R. C. Storr, and J. Rimmer, *J. C. S. Chem. Commun.*, 657 (1974).

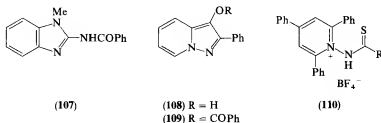
<sup>214</sup> J. J. Barr and R. C. Storr, *J. C. S. Perkin I*, 185 (1979).

is the major reaction type. Heating pyridine *N*-benzoylimine above its melting point ( $\sim 190$ – $200^\circ\text{C}$ ) causes the N—N bond fission with Curtius-type rearrangement to give pyridine and phenyl isocyanate which is isolated as diphenylurea.<sup>215</sup> It is reported that the decomposition temperature can be lowered by approximately  $100^\circ\text{C}$  in the presence of anhydrous copper(II) chloride which is shown to form an N-bonded complex with the *N*-imine.<sup>216</sup> Thermolysis of 2,4,6-triphenylpyridine *N*-benzoylimine at  $220^\circ\text{C}$  permits isolation, in high yield, of phenyl isocyanate; this provides a new general method for the preparation of aryl isocyanates (Eq. 38).<sup>87,88</sup>



Interestingly, 1-methylbenzimidazole 3-benzoylimine gives rearranged product **107**, in addition to the N—N bond cleavage products.<sup>122</sup> A diaziridine intermediate has been proposed to account for the formation of **107**. A similar rearrangement occurs with phthalazine 2-benzoylimine.<sup>217</sup> Thermolysis of 2-benzoyloxymethylpyridine *N*-benzoylimine affords 3-hydroxypyrazolo[1,5-*a*]pyridine **108** as the major product along with small amounts of the 3-benzoyloxy derivative **109**.<sup>142</sup>

Thermolysis of benzo[*c*]cinnoline *N*-acylimines gives the *N*-acylcinnolines and benzo[*c*]cinnoline.<sup>44</sup>



#### 4. *N*-Thioacylimines

Thermolysis of *N*-thioacylamino-2,4,6-triphenylpyridinium salts (**110**) leads to complete decomposition. Heating the salts with triphenylpyridine gives the nitriles (RCN) by loss of sulfur.<sup>88</sup>

<sup>215</sup> Y. Tamura, H. Ishibashi, N. Tsujimoto, and M. Ikeda, *Chem. Pharm. Bull.* **19**, 1285 (1971).

<sup>216</sup> L. Y. Chia, S. A. Dias, and W. R. McWhinnie, *J. Inorg. Nucl. Chem.* **38**, 1263 (1976).

<sup>217</sup> K. Lempert and K. Zauer, *Acta Chim. Acad. Sci. Hung.* **88**, 81 (1976).

## E. PHOTOCHEMICAL REACTIONS

To date, several types of photochemical reactions of heteroaromatic *N*-imines have been revealed. The typical reaction types are (i) ring enlargement to 1,2-diazepine derivatives, (ii) ring enlargement to 1,3-diazepine derivatives, (iii) 1,2-migration of the imino nitrogen, and (iv) *N*—*N* bond scission. The reaction courses are markedly affected by the nature of the parent heterocycles and substituents on the imino nitrogen. Consequently, this section is arranged according to the heteroaromatics. This area has been recently reviewed.<sup>218–220</sup>

1. Pyridine *N*-Imines

The formation of (1*H*)-1,2-diazepines by ring enlargement of pyridine *N*-acylimines has been discovered independently by three groups<sup>221–223</sup> and explored thoroughly. This reaction is now recognized as a very general and important reaction type.

Pyridine *N*-benzoylimine,<sup>21,27,28,126,224,225</sup> *N*-acetylimine,<sup>27,69,116,221,223,225,226</sup> *N*-alkoxycarbonylimines,<sup>20,21,69,116,221,222,224,227–232</sup> and *N*-sulfonylimines<sup>21,127,224</sup> can be transformed into the corresponding 1,2-diazepines in high yields. This photorearrangement of pyridine *N*-acylimines has been postulated to proceed via the 1,7-diazanorcaradienes **111** which could result from a photoinduced electrocyclic reaction of the 1,3-dipoles. A thermally allowed disrotatory ring opening should then lead to the 1,2-diazepines (Eq. 39). Although such intermediates have not yet been detected so far by any spectroscopic and chemical means, the proposed mechanistic

<sup>218</sup> M. Nastasi, *Heterocycles* **4**, 1509 (1976).

<sup>219</sup> J. Streith, *Heterocycles* **6**, 2021 (1977).

<sup>220</sup> J. Streith, *Pure Appl. Chem.* **49**, 305 (1977).

<sup>221</sup> J. Streith and J. M. Cassal, *Angew. Chem., Int. Ed. Engl.* **7**, 129 (1968).

<sup>222</sup> T. Sasaki, K. Kanematsu, and A. Kakehi, *Chem. Commun.*, 432 (1969).

<sup>223</sup> V. Snieckus, *Chem. Commun.*, 831 (1969).

<sup>224</sup> J. Streith and J.-M. Cassal, *Tetrahedron Lett.*, 4541 (1968).

<sup>225</sup> J. Streith and J.-L. Schuppiser, *Tetrahedron Lett.*, 4859 (1976).

<sup>226</sup> A. J. Carty, G. Kan, D. P. Madden, V. Snieckus, M. Stanton, and T. Birchall, *J. Organomet. Chem.* **32**, 241 (1971).

<sup>227</sup> J. Streith and J.-M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).

<sup>228</sup> J. Streith, A. Blind, J.-M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969).

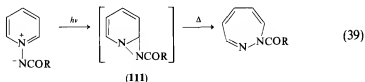
<sup>229</sup> M. Nastasi, and J. Streith, *Bull. Soc. Chim. Fr.*, 630 (1973).

<sup>230</sup> R. Allmann, A. Frankowski, and J. Streith, *Tetrahedron* **28**, 581 (1972).

<sup>231</sup> T. Tsuchiya, H. Arai, H. Hasegawa, and H. Igeta, *Chem. Pharm. Bull.* **25**, 2749 (1979).

<sup>232</sup> T. Tsuchiya, J. Kurita, and H. Kojima, *J. C. S. Chem. Commun.*, 444 (1980).

scheme has now been supported by the recent extensive studies by Streith and co-workers.<sup>219,220,233,234</sup> Experiments carried out so far suggest that the ring-expansion reaction proceeds via the first excited singlet state, which is assigned to the  $\pi \rightarrow \pi^*$  transition.<sup>69,125,220</sup>



In order to see the effect of the ring substituents on the photorearrangement, the behavior of a series of monosubstituted pyridine *N*-acylimines has been investigated. The results are briefly summarized as follows:

(1) The mesomeric effect of the substituent at the 4-position is very important: electron-donating groups ( $\text{NMe}_2$ , Cl, and Ph) allow the ring expansion to 1,2-diazepines, whereas strong electron-attracting groups ( $\text{COAr}$ ,  $\text{CO}_2\text{Et}$ , and CN) prohibit this reaction.<sup>20,21,69,221,224,227</sup> It is suggested that photochemical stability of the latter compounds is associated with the contribution of intramolecular charge-transfer states (see Section III,D).<sup>21</sup>

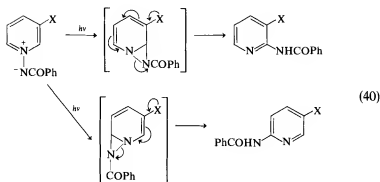
(2) The substituents (CN and Me) at the 2-position lead to regiospecific ring enlargement to the corresponding 3-substituted 1,2-diazepines, presumably because of a steric effect which would prevent ring closure of the imino nitrogen toward the C-2 position.<sup>20,21,27,221,224,227</sup>

(3) The electron-attracting groups ( $\text{CO}_2\text{Et}$ , CN,  $\text{CONH}_2$ ) at the 3-position show a strong directing effect on this photorearrangement to give 4-substituted 1,2-diazepines, while the electron-donating groups (Me,  $\text{OCOPh}$ , and halogens) show little orienting effect, to lead to a mixture of 4- and 6-substituted 1,2-diazepines.<sup>28,225</sup> These observations have been explained in terms of a simple Hückel molecular orbital (HMO) model.<sup>28</sup>

(4) The electron-donating substituents bearing acidic hydrogen atoms ( $\text{OH}$ ,  $\text{NH}_2$ , and  $\text{NHCOPh}$ ) do not lead to the 1,2-diazepines, but give a mixture of two isomeric 2-aminopyridines. One possible explanation would involve a nonregiospecific electrocyclozation to 1,7-diazanorcaradienes which undergo a fast and preferential cleavage of the N—N bond by a "push-pull" mechanism (Eq. 40).<sup>28</sup>

<sup>233</sup> H. Kwart, D. A. Benko, J. Streith, D. J. Harris, and J. L. Schuppiser, *J. Am. Chem. Soc.* **100**, 6501 (1978).

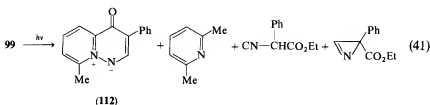
<sup>234</sup> H. Kwart, D. A. Benko, J. Streith, and J. L. Schuppiser, *J. Am. Chem. Soc.* **100**, 6502 (1978).



The N—N bond cleavage usually occurs only as a minor reaction course in pyridine *N*-acylimines. However, irradiation of pyridine *N*-acylimines in the presence of triplet sensitizers such as eosine leads to a notable increase of the N—N bond fission to give pyridine and the products derived from nitrenes.<sup>69,235</sup> On this basis, it is concluded that the N—N bond cleavage reaction takes place via an excited triplet state.

In the photolysis of *N*-thiocarbonylimines<sup>236</sup> and *N*-phenylimines,<sup>237</sup> the N—N bond scission is the exclusive reaction course. Irradiation of pyridine *N*-imidoylimine **105** in benzene affords oxadiazole **106** and pyridine (see also Section IV,D,2).<sup>60</sup>

An interesting new reaction mode of pyridine *N*-imines emerges when 2,6-dimethylpyridine *N*-vinylimine **99** is irradiated in benzene, affording a six-membered betaine **112**, along with 2,6-lutidine, an isonitrile, and an azirine (Eq. 41).<sup>56</sup>



## 2. Quinoline *N*-Imines and Related Fused Pyridine *N*-Imines

Irradiation of dimers derived from quinoline *N*-imines in methylene chloride containing acetic acid affords 1*H*-1,2-benzodiazepines **113** in moderate yields, together with small amounts of 2-aminoquinolines and the

<sup>235</sup> M. Nastassi, H. Strub, and J. Streith, *Tetrahedron Lett.*, 4719 (1976).

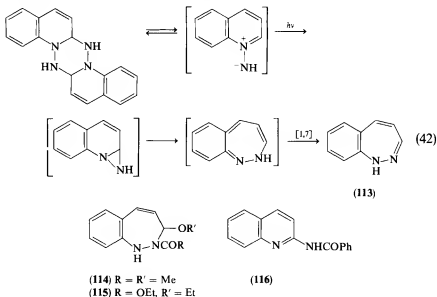
<sup>236</sup> K. T. Potts and R. Dugas, *Chem. Commun.*, 732 (1970).

<sup>237</sup> V. Snieckus and G. Kan, *Chem. Commun.*, 172 (1970).

parent quinolines.<sup>29,238</sup> The electron-donating substituents (4-Me, 7-Me, and 7-OMe) at C-4 and C-7 provide good yields of the benzodiazepines, whereas both electron-donating and -withdrawing groups (6-Me, 6-OMe, 6-Cl, and 6-CO<sub>2</sub>Me) at C-6 give lower or poor yields of products. Attempts to obtain benzodiazepines from other 2- and 4-substituted quinolines (2-Me, 2-Cl, 2-Ph, 4-Cl, 4-NO<sub>2</sub>, and 4-OMe) have not succeeded.

NMR studies in a CDCl<sub>3</sub>-acetic acid solution clearly demonstrated an equilibrium between the dimers and the corresponding *N*-imines. Based on this observation, a mechanism for the formation of the 1,2-benzodiazepines via the diaziridines and *o*-quinonoid 2*H*-1,2-benzodiazepine intermediates is proposed. Considering their aromatic stability, the latter would be expected to undergo a photochemically allowed [1,7]-sigmatropic hydrogen shift to give the observed product (Eq. 42).

Irradiation of quinoline *N*-acetyl-<sup>239</sup> and *N*-ethoxycarbonylimines<sup>215,240</sup> in alcoholic solvents gives 2,3-dihydro-1*H*-1,2-benzodiazepines **114** and **115**, respectively, as the major products. In these cases *o*-quinonoid 2*H*-1,2-benzodiazepine intermediates are stabilized by incorporation of the solvent. Quinoline *N*-benzoylimine on irradiation in methanol yields exclusively 2-benzoylaminoquinoline (**116**).<sup>215,240</sup>



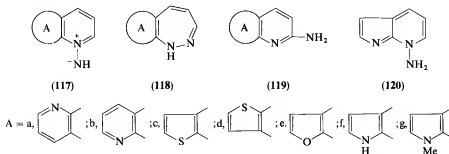
<sup>238</sup> T. Tsuchiya, J. Kurita, H. Igeta, and V. Snieckus, *J. C. S. Chem. Commun.*, 640 (1974).

<sup>239</sup> T. Shiba, K. Yamane, and H. Kato, *Chem. Commun.*, 1592 (1970).

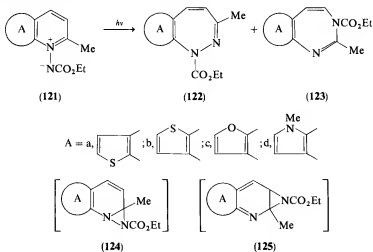
<sup>240</sup> Y. Tamura, S. Matsugashita, H. Ishibashi, and M. Ikeda, *Tetrahedron* **29**, 2359 (1973).



The fused pyridine *N*-imines **117a–e** or their dimers show photochemical behavior very similar to that of quinoline *N*-imines, and thus the corresponding fused 1*H*-1,2-diazepines **118**, along with small amounts of 2-aminopyridine derivatives **119**, are obtained. However, an analogous route to the pyrrolo-diazepine **118f** is unsuccessful because the *N*-imine **117f** tautomerizes rapidly to 7-amino-7*H*-7-azaindole **120**, which is photochemically stable. The *N*-imine **117g**, upon irradiation, yields the corresponding diazepine **118g** which gradually decomposes and cannot be isolated.<sup>32,241</sup>



Irradiation of the corresponding *N*-acylimines gives only 2-acylamino-pyridine derivatives. However, the 2-methyl congeners **121** give 1*H*-1,2-diazepines **122** and 3*H*-1,3-diazepines **123**.<sup>242</sup> The formation of **123** involves ring expansion of the diaziridine intermediate **125** formed via **124** by a [1,5]-sigmatropic shift of the nitrogen atom.

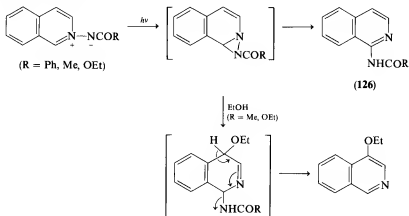


<sup>241</sup> T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Heterocycles* **9**, 621 (1978).

<sup>242</sup> T. Tsuchiya, M. Enkaku, and S. Okajima, *J. C. S. Chem. Commun.*, 454 (1980).

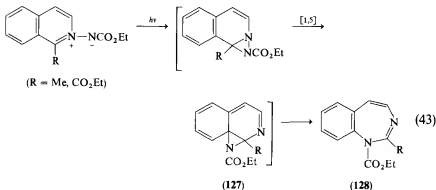
## 3. Isoquinoline N-Imines and Related Fused Pyridine N-Imines

Isoquinoline *N*-ethoxycarbonyl-, *N*-acetyl-, and *N*-benzoylimines are converted into the corresponding 1-acylaminoisoquinolines **126**.<sup>78,215,240,243</sup> Irradiation of the *N*-acetyl- and *N*-ethoxycarbonylimines in ethanol gives 4-ethoxyisoquinoline in addition to **126**. The proposed mechanism is shown in Scheme 8.



SCHEME 8

In contrast, photolysis of 1-substituted isoquinoline *N*-ethoxycarbonylimines in methylene chloride gives the 1*H*-1,3-benzodiazepines **128** in approximately 20% yields.<sup>244</sup> The formation of the diazepines may involve a ring expansion of the diaziridine intermediates **127** (Eq. 43).

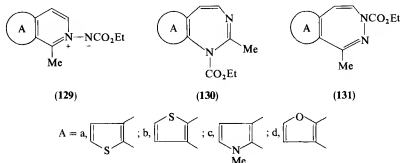


<sup>243</sup> J. Becker and C. Lohse, *Acta Chem. Scand.* **26**, 4041 (1972).

<sup>244</sup> T. Tsuchiya, M. Enkaku, J. Kurita, and H. Sawanishi, *J. C. S. Chem. Commun.*, 534 (1979); T. Tsuchiya, M. Enkaku, and S. Okajima, *Chem. Pharm. Bull.*, **28**, 2602 (1980).

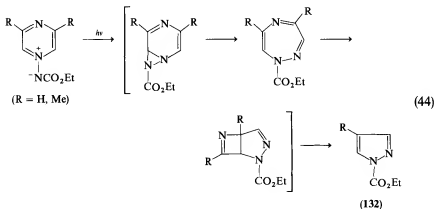
An attempt to prepare 2,3-benzodiazepines from *N*-aminoisoquinolinium salts has not been successful.<sup>29</sup>

Photochemical behavior of the related fused pyridine *N*-acylimines **129** has also been studied. Pyrrolo- and thienopyridine *N*-ethoxycarbonylimines **129a-c** give 1*H*-1,2-diazepines **130** and 3*H*-2,3-diazepines **131**, whereas furopyridine *N*-ethoxycarbonylimine **129d** gives only 3*H*-2,3-diazepine **131**.<sup>245</sup>



#### 4. Diazine *N*-Acylimines

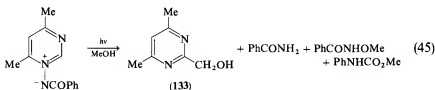
Pyrazine *N*-ethoxycarbonylimines, when irradiated in acetone, afford pyrazoles **132** and the parent pyrazines.<sup>246</sup> The formation of **132** may involve initial ring expansion to the 1,2,5-triazepines via the diaziridine intermediates. The triazepines may then isomerize to the bicyclic valence isomers, followed by extrusion of RCN to produce **132** (Eq. 44).



<sup>245</sup> T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Heterocycles* **12**, 1471 (1979).

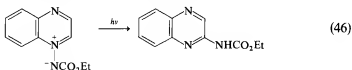
<sup>246</sup> T. Tsuchiya, J. Kurita, and K. Ogawa, *J. C. S. Chem. Commun.*, 250 (1976).

Irradiation of pyrimidine *N*-benzoylimine in methanol has been reported to give **133** and secondary products derived from benzoyl nitrene (Eq. 45).<sup>247</sup>



### 5. Benzodiazine *N*-Acylimines

Irradiation of quinoxaline 1-acylimines gives 2-acylaminoquinoxalines (Eq. 46).<sup>65</sup> 1,4-Diphenylphthalazine 2-benzoylimine, when irradiated in various deaerated solvents, affords a mixture of tarry products which, in some cases, contains small amounts of diphenylphthalazine.<sup>217</sup> When the same compound is irradiated in dichloromethane in the presence of air, *o*-dibenzoylbenzene is formed as the result of a photooxidation process (Eq. 47). This behavior parallels that of the corresponding *N*-oxide.<sup>248</sup> In contrast, photochemical behavior of quinazoline 3-acylimines is rather complex and markedly affected by the nature of the substituents present in the starting 3-acylimines.<sup>249–253</sup> For example, irradiation of **134** in ethanol gives four products (Eq. 48), whereas **135**, on irradiation in ethanol affords four products (Eq. 49). The formation of **136** is assumed to proceed by tautomerization of the starting *N*-acylimine into 4-methylene-3,4-dihydroquinazoline isomer and a subsequent [1,3]-shift of the ethoxycarbonlamino group from nitrogen to the exocyclic methylene carbon atom.



<sup>247</sup> F. Roeterdink and H. C. van Der Plas, *Recl. Trav. Chim. Pays-Bas* **96**, 156 (1977).

<sup>248</sup> K. B. Tomer, N. Harrit, I. Rosenthal, O. Buchardt, P. L. Kumler, and D. Creed, *J. Am. Chem. Soc.* **95**, 7402 (1973).

<sup>249</sup> J. Fetter, K. Lempert, J. Möller, and G. Szalai, *Tetrahedron Lett.*, 2775 (1975).

<sup>250</sup> J. Fetter, K. Lempert, G. Barta-Szalai, J. Möller, and L. Párkányi, *Acta Chim. Acad. Sci. Hung.* **94**, 233 (1977).

<sup>251</sup> J. Fetter, K. Lempert, and J. Möller, *Acta Chim. Acad. Sci. Hung.* **88**, 435 (1976).

<sup>252</sup> J. Fetter, K. Lempert, and J. Möller, *Tetrahedron* **34**, 2557 (1978).

<sup>253</sup> G. Bartaszalai, J. Fekete, J. Fetter, K. Lempert, and J. Möller, *Acta Chem. Scand.* **B33**, 79 (1979).



### 8. Five-Membered Heteroaromatic N'-Substituted N-Imines

The major reaction of five-membered heteroaromatic *N*-imines (1-alkyl-1,2,4-triazole 4-acylimines<sup>254</sup> and 4-arylimines,<sup>255</sup> 2-phenylbenzotriazole 1-cyanoimine,<sup>97</sup> thiazole *N*-acetylimine,<sup>239</sup> and 1-alkylbenzimidazole 3-acylimines<sup>122</sup>) is N—N bond fission, with a few exceptions. In the case of 1-methylbenzimidazole *N*-ethoxycarbonylimine, a 1,2-migration of the ethoxycarbonylamino group has been observed.<sup>122</sup>

## F. OXIDATION

Oxidative N—N bond cleavage with 30% hydrogen peroxide has been reported for pyridine *N*-phenylimines to give pyridine and nitrobenzenes, together with the other minor products.<sup>148</sup> *N*-Aminoquinolinium salt is deaminated by treating with 30% hydrogen peroxide in acetic acid.<sup>256</sup> The reaction of triphenylpyridine *N*-phenylimine with hydroperoxides, giving 1,6-dihydropyridazines, has already been described (Section IV,B,5). The N—N bond of 2,4-diphenyl-6-methylpyridine *N*-acylimines and 1-alkyl-1,2,4-triazole 4-(*p*-nitrophenyl)imines is cleaved by ozone.<sup>257</sup> Photolysis of an oxygenated benzene solution of 2,4,6-triphenylpyridine *N*-phenylimine is reported to give azoxybenzene (15%) and a minor amount of 2-benzoyl-3,5-diphenylpyrrole, in addition to aniline and 2,4,6-triphenylpyridine which are the major products of anaerobic photolysis.<sup>257</sup>

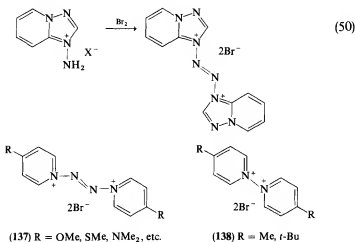
Glover and co-workers have investigated oxidation of a variety of fused *N*-aminoimidazolium and -triazolium salts with aqueous bromine giving tetrazenes (Eq. 50) because some of the tetrazenes show useful neuromuscular blocking activity of the nondepolarizing type.<sup>19,38-41,107,108,113</sup> Similar oxidation of 4-substituted (NMe<sub>2</sub>, OMe, SMe) *N*-aminopyridinium salts yields the corresponding 1,1'-azopyridinium salts **137**, whereas 4-*t*-butyl and 4-methyl derivatives give 1-pyridiniopyridinium salts **138**.<sup>41</sup> It is suggested that the reaction involves aminonitrenes as intermediates. Mesomeric delocalization of the charge on the quaternary center may be important for the formation of the tetrazenes. The mechanism of the formation of **138** is not clear.

<sup>254</sup> H.-J. Timpe and H. G. O. Becker, *J. Prakt. Chem.* [2] **314**, 325 (1972).

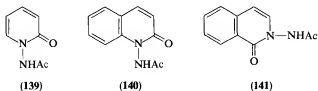
<sup>255</sup> C. W. Bird, D. Y. Wong, G. V. Boyd, and A. J. H. Summers, *Tetrahedron Lett.*, 3187 (1971).

<sup>256</sup> H. Itokawa, S. Kameyama, T. Inaba, T. Tazaki, R. Haruta, Y. Kawazoe, and M. Maeda, *Chem. Pharm. Bull.* **26**, 1015 (1978).

<sup>257</sup> C. W. Bird and M. A. Sheikh, *Tetrahedron Lett.*, 1333 (1975).



Oxidation of *N*-aminopyridinium, *N*-aminoquinolinium, and *N*-aminoisoquinolinium bromides with lead tetraacetate in acetic acid affords 1-acetamido-2-pyridone (**139**), 1-acetamido-2-quinolone (**140**), and 2-acetamido-1-isoquinolone (**141**), respectively.<sup>42</sup> A similar oxidation is reported to occur with 2-aminoimidazopyridinium salts.<sup>258</sup> There is good evidence that the oxidation implicates the bromide ion.<sup>42</sup>



## G. REDUCTION

A variety of methods have been reported for the reductive N—N bond cleavage: catalytic hydrogenolysis,<sup>44,62,100,104</sup> zinc-acetic acid,<sup>259</sup> stannous chloride in hydrochloric acid,<sup>98</sup> *O,O*-dialkyl dithiophosphoric acid,<sup>260</sup> tri-*n*-butyltin hydride,<sup>261</sup> and electrochemical reduction.<sup>262</sup>

<sup>258</sup> E. E. Glover, L. W. Peck, and D. G. Doughthy, *J. C. S. Perkin I*, 1833 (1979).

<sup>259</sup> H.-J. Timpe, *Z. Chem.* **12**, 333 (1972).

<sup>260</sup> S. Oae, A. Nakanishi, and N. Tsujimoto, *Tetrahedron* **28**, 2981 (1972).

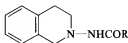
<sup>261</sup> S. Kozuka, T. Akasaka, S. Furumai, and S. Oae, *Chem. Ind. (London)*, 452 (1974).

<sup>262</sup> H. Lund and S. K. Sharma, *Acta Chem. Scand.* **26**, 2329 (1972).

Sodium borohydride reduction of pyridine *N*-acylimines<sup>15,73,263,264</sup> and isoquinoline *N*-acylimines<sup>265</sup> gives the corresponding tetrahydro derivatives **142** and **143** in good yields. A similar reduction of the hydroiodides of 4-methylquinoline *N*-imine and *N*-methoxycarbonylimine leads to 1,2-dihydro derivatives **144**.<sup>238</sup>



(142)



(143)



(144)

An interesting application of heteroaromatic *N*-imines involves dehydrogenation of piperidine, anabasine, and Hantzsch ester.<sup>266-269</sup>

## H. METALLATION REACTION

Metalation of pyridine *N*-benzoylimine by palladium(II), platinum(II), rhodium(III), and iridium(III) chlorides affords metal-*N*-imine complexes, e.g.,  $[(\text{PdLCl})_2]$ ,  $[\text{PtL}_2]$ ,  $[\text{RhL}_2(\text{H}_2\text{O})_2]\text{Cl}$ , and  $[\text{IrL}_2(\text{H}_2\text{O})\text{Cl}] \cdot 3\text{H}_2\text{O}$ , where L is  $\text{C}_6\text{H}_5\text{N}^+\text{N}^-\text{COPh}$ .<sup>130</sup> Spectroscopic data show that the phenyl ring is metallated in a position ortho to the carbonyl group and that the *N*-imine is coordinated through the imino nitrogen. There is good evidence to indicate that the mechanism of the reaction involves preliminary coordination of the *N*-imine followed by intramolecular electrophilic attack by the metal.

The reaction of pyridine *N*-acetyl- and *N*-propionylimines ( $=\text{L}$ ) with palladium(II) chloride gives simple coordination compounds  $[\text{PdL}_2\text{Cl}_2]$ . Both pyridine *N*-benzenesulfonyl- and *N*-benzoylimines ( $=\text{L}$ ) also give coordination compounds  $\text{ML}_4(\text{ClO}_4)_2$  with cobalt(II) and copper(II).<sup>216</sup>

<sup>263</sup> T. Tsuchiya and H. Sashida, *Heterocycles* **12**, 1453 (1979).

<sup>264</sup> T. Tsuchiya, H. Sashida, and H. Sawanishi, *Chem. Pharm. Bull.* **26**, 2880 (1978).

<sup>265</sup> K. Redda, L. A. Corleto, and E. E. Knaus, *J. Med. Chem.* **22**, 1079 (1979).

<sup>266</sup> S. V. Zalyalieva, Yu. V. Kurbatov, O. S. Otroshchenko, A. S. Sadykov, and R. Azzamova, *Khim. Geterotsikl. Soedin.*, 816 (1973) [*CA* **79**, 92449 (1973)].

<sup>267</sup> Yu. V. Kurbatov, S. V. Zalyalieva, O. S. Otroshchenko, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.*, 225 (1975) [*CA* **82**, 170623 (1975)].

<sup>268</sup> S. V. Zalyalieva, Yu. V. Kurbatov, O. S. Otroshchenko, and A. S. Sadykov, *Khim. Geterotsikl. Soedin.*, 226 (1976) [*CA* **85**, 32781 (1976)].

<sup>269</sup> Yu. V. Kurbatov and S. V. Zalyalieva, *Khim. Geterotsikl. Soedin.*, 1535 (1977) [*CA* **88**, 74275 (1978)].



## I. RADICAL REACTION

There is only one published example of this type of reaction. Treatment of *N*-aminoquinolinium salts with *t*-butylperoxide in the presence of ferrous sulfate gives *N*-amino-2-methylquinolinium salt (18.4%) together with quinoline (45.5%), 2-methylquinoline (6.2%), and 2,4-dimethylquinoline (3.6%).<sup>256</sup>

## V. Survey of Ring Systems

The following is a list of sections (given in brackets) and references (given in parentheses) which are indexed according to the parent heterocycles with the exception of pyridine.

## A. HETEROAROMATICS WITH ONE NITROGEN ATOM

## 1. Quinoline

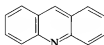


[II,A,1] (5, 6, 10, 14, 17, 29-31, 42, 240); [II,A,2] (50); [III,C] (240); [III,D] (131, 240); [III,E] (17, 29, 131); [III,F] (131, 240); [IV,A,1] (14, 17, 240); [IV,A,2] (61); [IV,A,6] (30); [IV,A,5] (163, 165); [IV,B,2] (14); [IV,C] (14, 17, 190, 191); [IV,D] (215); [IV,E] (29, 215, 238-240); [IV,F] (42, 256); [IV,G] (238); [IV,I] (256).

## 2. Isoquinoline



[II,A,1] (6, 17, 42, 160, 240, 243); [II,A,2] (50); [II,B,1] (71, 72, 78, 79); [II,B,3] (94); [III,C] (78, 79, 240); [III,D] (79, 131, 191, 240); [III,E] (17, 78, 79, 131); [III,F] (131, 134, 137); [III,G] (17); [IV,A,1] (17, 78, 79, 209, 240, 243); [IV,A,2] (61); [IV,A,5] (160); [IV,A,6] (163, 165); [IV,C] (17, 79, 190); [IV,D] (57, 209, 215); [IV,E] (79, 215, 240, 243, 244); [IV,F] (42); [IV,G] (265).

3. *Acridine*

[II,A,1] (12, 35); [II,A,2] (50); [IV,A,1] (35); [IV,B,1] (35).

4. *Phenanthridine*

[II,A,1] (17, 33, 34); [II,A,2] (50); [III,C] (33, 34); [III,E] (33, 34); [III,F] (34); [IV,C] (17, 33, 202); [IV,E] (34).

## B. HETEROAROMATICS WITH TWO NITROGEN ATOMS IN THE SAME RING

1. *1-Substituted Pyrazoles*

[II,A,1] (36, 37); [IV,A,5] (36, 37).

2. *1-Substituted Imidazole*

[II,A,1] (122, 142); [II,C] (107); [III,C] (122); [III,D] (122); [III,E] (122); [III,F] (122); [IV,A,1] (122, 142); [IV,F] (107).

3. *Pyridazine*

[II,A,1] (6, 9, 144, 189); [IV,A,1] (9, 144, 189); [IV,C] (9, 188, 189, 194, 195).

4. *Pyrimidine*

[II,A,1] (9, 144); [IV,A,1] (9, 144, 247); [IV,C] (9); [IV,E] (247).

5. *Pyrazine*

[II,A,1] (9, 31, 144); [IV,A,1] (9, 144); [IV,C] (9); [IV,E] (246).

6. *1-Substituted 1H-Indazole*

[II,A,1] (36); [IV,A,1] (36); [IV,C] (36).

7. *Imidazo[1,2-a]pyridine*

[II,A,1] (19); [II,B,3] (19); [II,D] (19); [IV,F] (19).

8. *Imidazo[1,5-a]pyridine*

[IV,F] (258).

9. *1-Substituted 1H-Benzimidazole*

[II,A,1] (39, 122, 147, 203); [II,C] (108); [III,C] (122); [III,D] (122); [III,E] (122); [III,F] (122); [III,H] (122); [IV,A,1] (122, 147); [IV,A,5] (151); [IV,C] (151, 203, 207); [IV,D] (122); [IV,E] (122); [IV,F] (39, 108).

10. *Cinnoline (1-Imine)*

[II,A,1] (131); [III,D] (131); [III,E] (131); [III,F] (131); [IV,C] (188).

11. *Quinazoline (1-Imine)*

[II,A,1] (11, 131); [III,D] (131); [III,E] (131); [III,F] (131); [IV,A,1] (131); [IV,B,1] (131, 177); [IV,B,2] (177); [IV,C] (177, 190).

12. *Quinazoline (3-Imine)*

[II,B,3] (100); [III,E] (100); [III,F] (100); [IV,B,3] (178); [IV,C] (100); [IV,E] (249–253); [IV,G] (100).

13. *Quinoxaline*

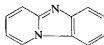
[II,A,1] (131); [II,A,2] (65); [III,D] (131); [III,E] (131); [III,F] (131);  
[IV,A,1] (131); [IV,B,1] (177); [IV,B,2] (177); [IV,C] (177, 190); [IV,E] (65).

14. *Phthalazine*

[II,A,1] (131, 217); [III,D] (131); [III,E] (131); [III,F] (131); [IV,A,1]  
(131); [IV,B,1] (177); [IV,B,2] (177); [IV,C] (177, 190); [IV,E] (217).

15. *Benz[cd]indazole*

[II,B,3] (106); [III,F] (106); [IV,D] (106); [IV,E] (106); [IV,G] (106).

16. *Pyrido[1,2-a]benzimidazole*

[II,A,1] (39); [IV,F] (39).

17. *Benzo[c]cinnoline*

[II,A,1] (44); [II,B,3] (44, 101–105); [IV,A,1] (44, 104, 214); [IV,A,3] (44);  
[IV,A,5] (44); [IV,A,7] (168); [IV,C] (196–201); [IV,D] (44, 201, 211, 213,  
214); [IV,E] (44); [IV,G] (44, 104).

## C. HETEROAROMATICS WITH TWO NITROGEN ATOMS IN A DIFFERENT RING

1. *1H-Pyrrolo*[2,3-*b*]pyridine

[II,A,1] (32); [IV,E] (32).

2. *1H-Pyrrolo*[3,2-*b*]pyridine

[II,A,1] (242); [IV,E] (242).

3. *1H-Pyrrolo*[2,3-*c*]pyridine

[II,A,1] (245); [IV,E] (245).

4. *1,5-Naphthyridine*

[II,A,1] (6, 32, 131, 241); [III,D] (131); [III,E] (131); [III,F] (131); [IV,A,1] (131); [IV,C] (190); [IV,E] (32, 241).

5. *1,8-Naphthyridine*

[II,A,1] (6, 32, 131, 241); [III,D] (131); [III,E] (131); [III,F] (131); [IV,A,1] (131); [IV,C] (190); [IV,E] (32, 241).

## D. HETEROAROMATICS WITH THREE NITROGEN ATOMS

1. *1-Substituted 1,2,3-Triazole*

[II,B,3] (95–97); [IV,C] (95–97); [IV,D] (95, 97); [IV,E] (95, 97).

2. *1-Substituted 1,2,4-Triazole (4-Imine)*

[II,B,3] (99); [II,C] (109–114); [II,D] (113); [III,C] (109, 110, 124); [III,D] (128); [III,E] (2, 132); [III,F] (135, 136); [III,H] (139); [IV,A,1] (132); [IV,A,2] (124); [IV,A,5] (139, 159); [IV,B,1] (111, 113); [IV,C] (204, 205); [IV,E] (110, 135, 254, 255, 257); [IV,F] (113, 257); [IV,G] (259).

3. *2-Substituted 2H-Benzotriazole*

[II,B,3] (97, 98); [III,C] (98); [III,D] (98); [IV,D] (97); [IV,E] (97).

4. *1-Substituted 1H-Benzotriazole (3-Amine Salt)*

[II,C] (113); [IV,F] (113).

5. *1,2,4-Triazolo[1,5-a]pyridine (1-Amine Salt)*

[II,A,1] (39); [II,B] (39); [IV,F] (39).

6. *1,2,4-Triazolo[4,3-a]pyridine (1-Amine Salt)*

[II,A,1] (39); [IV,F] (39).

7. *1,2,4-Triazolo[4,3-a]pyridine (2-Amine Salt)*

[II,A,1] (39).

8. *Imidazo[1,2-a]pyrimidine (1-Amine Salt)*

[II,A,1] (40); [II,D] (40); [IV,A,5] (40); [IV,F] (40).

E. HETEROAROMATICS WITH NITROGEN ATOM(S)  
AND ANOTHER HETEROATOM1. *Thiazole*

[II,A,1] (142, 145, 146, 206); [IV,A,1] (142, 145, 146); [IV,A,5] (145, 146); [IV,C] (142, 206); [IV,E] (239).

2. *Benzothiazole*



[II,A,1] (143, 145, 152); [IV,A,1] (143, 145); [IV,A,5] (145, 152); [IV,C] (143).

3. *Thieno*[2,3-*b*]pyridine



[II,A,1] (32, 241); [IV,E] (32, 241, 242).

4. *Thieno*[3,2-*b*]pyridine



[II,A,1] (32, 241); [IV,E] (241, 242).

5. *Thieno*[2,3-*c*]pyridine



[II,A,1] (245); [IV,E] (245).

6. *Thieno*[3,2-*c*]pyridine



[II,A,1] (245); [IV,E] (245).

7. *Furo*[2,3-*b*]pyridine



[II,A,1] (32, 241); [IV,E] (241).

8. *Furo*[3,2-*b*]pyridine

[II,A,1] (241); [IV,E] (241, 242).

9. *Furo*[3,2-*c*]pyridine

[II,A,1] (245); [IV,E] (245).

10. *Thiadiazole*

[II,A,1] (147); [IV,A,1] (147).

11. *Imidazo*[2,1-*b*]thiazole

[II,A,1] (38); [IV,F] (38).

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# Mononuclear Heterocyclic Rearrangements

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DOMENICO SPINELLI

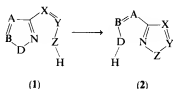
*Cattedra di Chimica Organica-Facoltà di Farmacia,  
Università di Bologna, Bologna, Italy*

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## I. Introduction

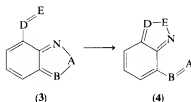
Many examples of heterocyclic synthesis by ring transformation have been known<sup>1</sup> for a long time, and they often involve a side chain. The reactive center in the side chain is frequently joined to the starting heterocycle through a continuous  $\pi$ -electron system. Ring conversions of type **1**  $\rightarrow$  **2** were just recognized by Boulton, Katritzky, and Hamid as a general class of rearrangement and designated as "monocyclic rearrangements of heterocycles."<sup>2</sup> We use the term "mononuclear heterocyclic rearrangement" (mhr).



<sup>1</sup> (a) H. C. van der Plas, "Ring Transformations of Heterocycles," Vols. 1 and 2. Academic Press, New York, 1973; (b) "Aromatic and Heteroaromatic Chemistry," Spec. Period. Reps., Vols. I-VI, Chemical Society, London.

<sup>2</sup> A. J. Boulton, A. R. Katritzky, and A. M. Hamid, *J. Chem. Soc. C*, 2005 (1967).

Rearrangements in the benzo-fused series have been similarly systematized as  $3 \rightarrow 4$ .<sup>3</sup>



These reactions cover many possible azole  $\rightarrow$  azole interconversions; the literature indicates that examples of mhrs are reported for only a limited number of ABD sequences. As pointed out by Boulton,<sup>4</sup> the present authors,<sup>5</sup> and by Katritzky *et al.*,<sup>6</sup> known conversions are limited to heterocycles containing an N—O bond (i.e., D = O in 1).

According to the electron densities calculated for isoxazole,<sup>7</sup> 1,2,4-oxadiazole,<sup>7,8</sup> and 1,2,5-oxadiazole,<sup>7</sup> the cleavage of the weak N—O bond (characterized<sup>9</sup> by a low  $\pi$ -character and a  $\sigma$ -density on O higher than on N) is also facilitated by the low aromaticity of these rings.<sup>10–12</sup> Consequently, the transformation  $1 \rightarrow 2$  is irreversible if  $Z \neq O$  because the final ring does not then contain the weak N—O bond. By contrast, if  $Z = O$ , the rearrangement can, in principle, be reversible. Moreover, if  $ABD = XYZ$ , the conversion is a mononuclear isoheterocyclic rearrangement, which is degenerate if substituents on AB are identical to those of XY.

Under the conditions used for the reactions,<sup>5</sup> Z must be a good nucleophilic site (its nucleophilicity can be increased by base catalysis or by the use of a suitable solvent). Accordingly, examples are known with Z being O, S, N, or C, and it has been suggested that it can also be Se.<sup>5</sup>

The present review covers the literature of conversions  $1 \rightarrow 2$  characterized by nucleophilic attack from a Z atom on an  $sp^2$ -nitrogen atom with displacement of atom D. On this basis, the known ring conversions are

<sup>3</sup> A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *Angew. Chem.* **76**, 816 (1964) [*Angew. Chem., Int. Ed. Engl.* **3**, 693 (1964)].

<sup>4</sup> A. J. Boulton, "Lectures in Heterocyclic Chemistry," Hetero Corporation, Provo, Utah, 1973.

<sup>5</sup> N. Vivona, G. Cusmano, M. Ruccia, and D. Spinelli, *J. Heterocycl. Chem.* **12**, 985 (1975).

<sup>6</sup> A. S. Afridi, A. R. Katritzky, and C. A. Ramsden, *J. C. S. Perkin I*, 315 (1976).

<sup>7</sup> M. Kamiya, *Bull. Chem. Soc. Jpn.* **43**, 3344 (1970).

<sup>8</sup> L. Paoloni and M. Cignitti, *Tetrahedron* **24**, 485 (1968).

<sup>9</sup> W. Adam and A. Grimison, *Theor. Chim. Acta* **7**, 342 (1967).

<sup>10</sup> C. Moussebois and J. F. M. Oth, *Helv. Chim. Acta* **47**, 942 (1964).

<sup>11</sup> G. Náray-Szabó and K. Horvath, *Croat. Chem. Acta* **49**, 461 (1977).

<sup>12</sup> M. J. Cook, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.* **17**, 255 (1974).

TABLE I  
 KNOWN RING CONVERSIONS

XYZ	Final ring	ABD	Starting ring	Section
CNO	1,2,5-Oxadiazole	NCO	1,2,4-Oxadiazole	II,A,1
		CCO	Isoxazole	II,A,2
		CNO	1,2,5-Oxadiazole	II,A,3
NCO	1,2,4-Oxadiazole	NCO	1,2,4-Oxadiazole	II,B,1
		CCO	Isoxazole	II,B,2
CCO	Isoxazole	NCO	1,2,4-Oxadiazole	II,C,1
		CNO	1,2,5-Oxadiazole	II,C,3
CNN	1,2,3-Triazole	NCO	1,2,4-Oxadiazole	II,D,1
		CCO	Isoxazole	II,D,2
		CNO	1,2,5-Oxadiazole	II,D,3
NCN	1,2,4-Triazole	NCO	1,2,4-Oxadiazole	II,E,1
		CCO	Isoxazole	II,E,2
		CNO	1,2,5-Oxadiazole	II,E,3
NCS	1,2,4-Thiadiazole	NCO	1,2,4-Oxadiazole	II,F,1
		CCO	Isoxazole	II,F,2
		CNO	1,2,5-Oxadiazole	II,F,3
NNN	Tetrazole	CCO	Isoxazole	II,G,2
NCC	Imidazole	NCO	1,2,4-Oxadiazole	II,H,1
CCN	Pyrazole	NCO	1,2,4-Oxadiazole	II,I,1
		CCO	Isoxazole	II,I,2

collected in Table I, which contains the following: XYZ sequence, final ring, ABD sequence, and starting ring. The material is divided by sections as a function of the XYZ sequence. Taking into account the reactivities observed in the rearrangements, available results are reported in each section in the following order: 1,2,4-oxadiazole, isoxazole, and 1,2,5-oxadiazole. For a detailed reactivity comparison, see Section II,E,4.

Finally, a short account with some examples is given of attempts at rearrangements involving a reaction center in **1** different from nitrogen, and of reactions involving a saturated side chain.

## II. Rearrangements

### A. REARRANGEMENTS INVOLVING SEQUENCE XYZ = CNO: FINAL RING 1,2,5-OXADIAZOLE

The sequence involves an oxime group in the side chain. In principle, this rearrangement should be reversible, but in practice no example of the reverse rearrangement has been reported (e.g., see Section II,B,3).

No attention has been paid to the geometries of the functional group; however, it should be understood that only if the oxime is *Z* (i.e., *cis* with respect to the ring in **5**) is there a pure mhr; if the oxime is *E* (i.e., *trans* with respect to the ring in **5**), the reaction presumably follows the pattern *E*-isomer  $\rightleftharpoons$  *Z*-isomer  $\rightarrow$  1,2,5-oxadiazole.



Because such a wide variety of experimental conditions have been used (acids, bases, metals at high temperatures), it is not practical to compare the available data in order to draw conclusions as to the effect of the rings and the side chain on the reaction. Systematic studies, thus far lacking, would be necessary. We report on the published data and give further details in cases where the reviewers have reinvestigated the reaction.

### 1. 1,2,4-Oxadiazole

The reported rearrangements have been achieved both by melting<sup>13,14</sup> the oxadiazole (**6**) [when 3-acylamino-1,2,5-oxadiazoles (**7**) are obtained] and by heating in hydrochloric acid<sup>13,15-17</sup> [when the 3-amino compounds (**9**) are produced, presumably via **7**]. No example of base-catalyzed rearrangements of oxime **6** has been reported. However, since the hydrolysis of *O*-acyl derivatives of oximes in basic solution is a well-known reaction<sup>13-15,18,19</sup> in the course of which no arrangement has ever been noticed, the above observation agrees with the hypothesis that the oximes thus formed, which are stable to bases, are *E*-isomers (see discussion on the behavior of *Z*- and *E*-oximes in Section II,A,2).

In some instances (depending on the substituents and the reaction conditions), the rearrangements of 1,2,4-oxadiazoles to 1,2,5-oxadiazoles occur in part or completely during the oximation of the starting ketones (**8**).<sup>14,19</sup>

<sup>13</sup> G. Ponzio and L. Avogadro, *Gazz. Chim. Ital.* **53**, 318 (1923).

<sup>14</sup> G. Ponzio, *Gazz. Chim. Ital.* **61**, 138 (1931).

<sup>15</sup> G. Ponzio and G. Ruggeri, *Gazz. Chim. Ital.* **53**, 297 (1923).

<sup>16</sup> C. Lehmann, E. Renk, and A. Gagneux, Swiss Patent 498,135 (1970) [*CA* **74**, 87992 (1971)].

<sup>17</sup> C. Lehmann, E. Renk, and A. Gagneux, Swiss Patent 498,855 (1970) [*CA* **74**, 112047 (1971)].

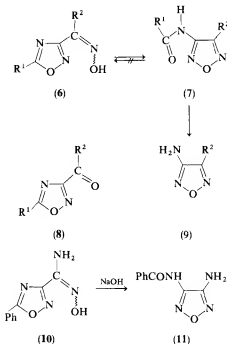
<sup>18</sup> S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.* **85**, 1686 (1955).

<sup>19</sup> S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.* **88**, 463 (1958).



A synthesis of 3-acylamino<sup>19,20</sup> and 3-amino-1,2,5-oxadiazoles<sup>21,22</sup> (assumed to proceed via intermediates **6** and/or **8**) has been achieved by reacting some 4-nitrosoimidazoles with hydroxylamine.

Amidoxime **10** rearranges to **11** by the action of sodium hydroxide.<sup>23</sup> It is known that the neutral amidoxime is the species that isomerizes, also at high pH.<sup>24</sup>



## 2. Isoxazole

Some oximes of 3-acylisoxazoles (**12**) rearrange to the corresponding 1,2,5-oxadiazole derivatives (**13**) on heating with aqueous potassium hydroxide, hydroxylamine hydrochloride, hydroxylamine,<sup>25-29</sup> or copper

<sup>20</sup> S. Cusmano and M. Ruccia, *Gazz. Chim. Ital.* **86**, 187 (1956).

<sup>21</sup> C. Lehmann, E. Renk, and A. Gagneux, Swiss Patent 498,134 (1970) [*CA* **74**, 87988 (1971)].

<sup>22</sup> C. Lehmann, E. Renk, and A. Gagneux, Swiss Patent 498,854 (1970) [*CA* **74**, 112049 (1971)].

<sup>23</sup> E. Durio and S. Dugone, *Gazz. Chim. Ital.* **66**, 139 (1936).

<sup>24</sup> K. J. Dignam and A. F. Hegarty, *J. C. S. Perkin II*, 1437 (1979).

<sup>25</sup> T. Ajello, *Gazz. Chim. Ital.* **67**, 55 (1937).

<sup>26</sup> T. Ajello, *Gazz. Chim. Ital.* **67**, 779 (1937).

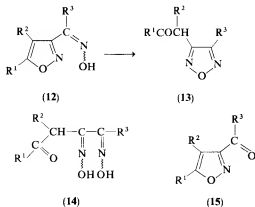
<sup>27</sup> T. Ajello and S. Cusmano, *Gazz. Chim. Ital.* **68**, 792 (1938).

<sup>28</sup> T. Ajello and S. Cusmano, *Gazz. Chim. Ital.* **69**, 391 (1939).

<sup>29</sup> T. Ajello, V. Sprio, and J. Fabra, *Ric. Sci., Parte 2: Sez. B* **4**, 575 (1964) [*CA* **62**, 547 (1965)].

powder.<sup>2</sup> It was reported by Ajello<sup>27</sup> that the rearrangements carried out in hydroxylic (aqueous) solvents proceed via open-chain polyoxime intermediates. In our opinion, the formation of an acyclic intermediate must be questioned, considering that compound **12** ( $R^1 = R^3 = \text{Me}$ ,  $R^2 = \text{H}$ ) did not rearrange even in aqueous potassium hydroxide in ethanol<sup>30</sup>—experimental conditions that would favor acyclic intermediates, but only by fusion with copper powder.<sup>2</sup>

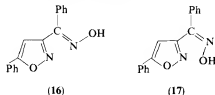
It has been claimed<sup>25-28</sup> that, depending on the substituents and experimental conditions, the oximation reaction of 3-acylisoxazoles (**15**) can give 1,2,5-oxadiazole derivatives directly. However, in some of the cases reported, a reinvestigation has failed to support this finding. Ajello<sup>26</sup> reported that 3-benzoyl-5-phenylisoxazole, when refluxed (3 h) with hydroxylamine hydrochloride in ethanol, gave a mixture of the oxime **12** ( $R^1 = R^3 = \text{Ph}$ ,  $R^2 = \text{H}$ ) and the 1,2,5-oxadiazole **13** ( $R^1 = R^3 = \text{Ph}$ ,  $R^2 = \text{H}$ ). When this was repeated,<sup>30</sup> only a mixture of *E*-(**16**) and *Z*-(**17**) oximes (ratio ~1:1, measured by NMR) was found. By the action of aqueous potassium hydroxide in ethanol, only the *Z*-isomer rearranged to the 1,2,5-oxadiazole **13** ( $R^1 = R^3 = \text{Ph}$ ,  $R^2 = \text{H}$ ); under the same experimental conditions the



$R^1 = \text{Me, Me, Ph, Ph, Ph, Ph}$

$R^2 = \text{H, H, H, H, Ph, COPh}$

$R^3 = \text{Me, Ph, Me, Ph, Ph, Ph}$

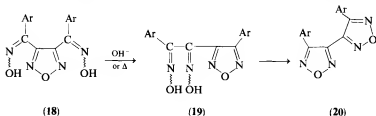


<sup>30</sup> N. Vivona and M. Ruccia, unpublished results.

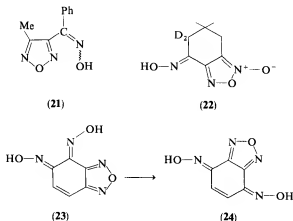
*E*-isomer **16** was practically unaffected.<sup>30</sup> This observation may explain Ajello's statement<sup>27</sup> that some oximes do not rearrange with potassium hydroxide.

### 3. 1,2,5-Oxadiazole

The first example of a ring conversion that can be classified as an iso-type mhr is the rearrangement of **18** to **19**, which could be dehydrated to **20**.<sup>31</sup>



Oximes **21** and **22**, and the furazan derived from **22**, were not rearranged.<sup>4</sup> It should be noted that an X-ray structure determination of **22** showed it to have the *E*-configuration, as shown.<sup>32</sup> In the benzo-fused series a similar rearrangement, **23** → **24**, has been reported.<sup>33,34</sup>



<sup>31</sup> G. Ponzio and F. Biglietti, *Gazz. Chim. Ital.* **63**, 159 (1933).

<sup>32</sup> M. Calleri, S. A. Chawdhury, and D. Viterbo, *Acta Crystallogr., Sect. B* **32**, 2678 (1976).

<sup>33</sup> D. Dal Monte, E. Sandri, and P. Mazzaracchio, *Boll. Sci. Fac. Chim. Ind. Bologna* **26**, 165 (1968) [*CA* **70**, 115074 (1969)].

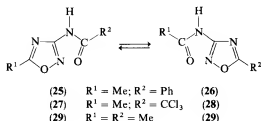
<sup>34</sup> A. S. Angeloni, V. Ceri, D. Dal Monte, E. Sandri, and G. Scapini, *Tetrahedron* **28**, 303 (1972).

B. REARRANGEMENTS INVOLVING SEQUENCE XYZ = NCO:  
FINAL RING 1,2,4-OXADIAZOLE

According to our previous statement (Section I), these rearrangements can be reversible; if the starting ring is a 1,2,4-oxadiazole, they are, by definition, isoheterocyclic.

1. 1,2,4-Oxadiazole

The following isoheterocyclic rearrangements have been studied<sup>5,35</sup>:



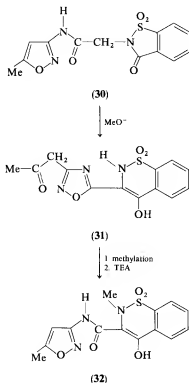
3-Benzoylamino-5-methyl-1,2,4-oxadiazole (**25**) and 3-acetylamino-5-phenyl-1,2,4-oxadiazole (**26**) heated at 180°C furnished an equilibrium mixture in which the second predominated<sup>5</sup> ( $[\text{26}]/[\text{25}] = \sim 6.4$ ). The same rearrangement has been realized in solution (strong base catalysis has been observed), and in this case the nature of the solvent affects the equilibrium position.<sup>5</sup> The likelihood of this rearrangement is connected with the nucleophilic power of the oxygen atom of the side chain. 3-Trichloroacetyl-amino-5-methyl-1,2,4-oxadiazole (**27**) did not rearrange to **28** either by heating above its melting point or by heating in DMSO (with or without catalytic potassium *t*-butoxide).

The degenerate rearrangement of 3-acetylamino-5-methyl-1,2,4-oxadiazole (**29**) has been investigated.<sup>35</sup> It was observed by NMR that the two methyl signals of **29** did not coalesce in DMSO up to 180°C, but the potassium salt of **29** gave coalescence of the methyl signals at 112°C ( $\Delta G^\ddagger = 19.9 \pm 0.4 \text{ kcal mol}^{-1}$ ). For this rearrangement the formation of a symmetrical anion as transition state or intermediate was suggested<sup>35</sup> (see Section III).

<sup>35</sup> N. Vivona, M. Ruccia, G. Cusmano, M. L. Marino, and D. Spinelli, *J. Heterocycl. Chem.* **12**, 1327 (1975).

## 2. Isoxazole

Some patents<sup>36</sup> have described the rearrangement of a 3-acylamino-5-methylisoxazole (**30**) into 5-substituted 3-acetonyl-1,2,4-oxadiazole **31**. The treatment of **30** with sodium methoxide produced an mhr as well as a ring expansion furnishing **31** which, in turn, by methylation followed by treatment with triethylamine, gave **32**, with a 1,2,4-oxadiazole  $\rightarrow$  isoxazole conversion (see Section II,C,1).



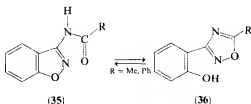
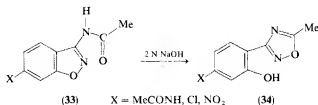
Some 3-acylamino-5-methylisoxazoles (**33**<sup>37,38</sup> and **35**<sup>39</sup>) rearranged to 5-substituted 3-(*o*-hydroxyphenyl)-1,2,4-oxadiazoles (**34** and **36**), but the driving force for this rearrangement is clearly different from that of the mhrs.

<sup>36</sup> A. C. Fabian, J. D. Genzer, C. F. Kasulanis, J. Shavel, and H. Zinnes, U.S. Patent 3,957,772 (1976) [*CA* **85**, 46725 (1976)]; U.S. Patent 3,978,073 (1976) [*CA* **86**, 16690 (1977)]; U.S. Patent 4,041,042 (1977) [*CA* **87**, 168068 (1977)]; U.S. Patent 4,018,762 (1977) [*CA* **87**, 53345 (1977)].

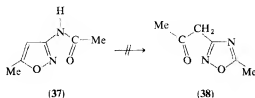
<sup>37</sup> H. Lindemann and H. Cissée, *Justus Liebigs Ann. Chem.* **469**, 44 (1929).

<sup>38</sup> H. Lindemann and H. Cissée, *J. Prakt. Chem.* [2] **122**, 232 (1929).

<sup>39</sup> K. Harsányi, *J. Heterocycl. Chem.* **10**, 957 (1973).



In fact, Boulton *et al.*<sup>2</sup> failed to convert 3-acetylamino-5-methylisoxazole (37) into 3-acetonyl-5-methyl-1,2,4-oxadiazole (38). This result is in apparent conflict with the rearrangement observed with 30.



### 3. 1,2,5-Oxadiazole

All attempts to effect this rearrangement have failed.<sup>2,4</sup> This observation agrees with the fact that the inverse reaction (from 1,2,4-oxadiazole to 1,2,5-oxadiazole) has been realized and found to be irreversible (see Section II,A,1).

## C. REARRANGEMENTS INVOLVING SEQUENCE XYZ = CCO: FINAL RING ISOXAZOLE

### 1. 1,2,4-Oxadiazole

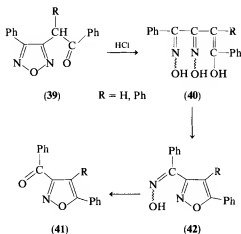
The literature on this rearrangement was examined in Section II,B,2 (see rearrangement of 31 and 36 to 32 and 35, respectively) when we were considering the conversion of isoxazole/NCO into 1,2,4-oxadiazole/CCO and vice versa.

## 2. Isoxazole

The mhr should be of the isoheterocyclic type; no example has been reported.

## 3. 1,2,5-Oxadiazole

It has been claimed<sup>40</sup> that ketones (39) rearrange to 3-acylisoxazole 41 in refluxing ethanolic hydrochloric acid via the reverse reaction of the rearrangement previously discussed (see Section II,A,2). However, it was later found that the starting materials were not oxadiazoles (39), but isoxazole oximes (42).<sup>30</sup>



## D. REARRANGEMENTS INVOLVING SEQUENCE XYZ = CNN: FINAL RING 1,2,3-TRIAZOLE

### 1. 1,2,4-Oxadiazole

Examples of this rearrangement that involve hydrazone as well as hydrazide side-chain units have been reported. Some arylhydrazones of 5-substituted 3-aryl-1,2,4-oxadiazoles (43) (see Table II) rearrange by heating at their melting point, or by refluxing with bases or acids, to 4-acylamino-2,5-di-aryl-1,2,3-triazoles (44).<sup>41-44</sup>

<sup>40</sup> S. Cusmano and S. Giambone, *Gazz. Chim. Ital.* **81**, 499 (1951).

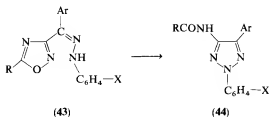
<sup>41</sup> M. Ruccia and D. Spinelli, *Gazz. Chim. Ital.* **89**, 1654 (1959).

<sup>42</sup> P. Gramantieri, *Gazz. Chim. Ital.* **65**, 102 (1935).

<sup>43</sup> T. Sasaki, T. Yoshioka, and Y. Suzuki, *Bull. Chem. Soc. Jpn.* **44**, 185 (1971).

<sup>44</sup> D. Spinelli, V. Frenna, A. Corrao, and N. Vivona, *J. C. S. Perkin II*, 19 (1978).

TABLE II

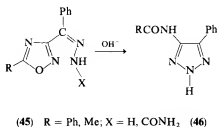


R	Ar	X	Experimental Conditions <sup>a</sup>	References
H	Ph	H	A, B <sup>b</sup>	41
Me	Ph	H	A, B, D <sup>b</sup>	41
Ph	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	H	A	42
Ph	Ph	H	A, B, D	41, 42
<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Ph	<i>p</i> -NO <sub>2</sub>	A, C	43
Ph	Ph	<i>p</i> -OMe	A	44
Ph	Ph	<i>p</i> -Me	A	44
Ph	Ph	<i>m</i> -Me	A	44
Ph	Ph	<i>p</i> -Cl	A	44
Ph	Ph	<i>p</i> -Br	A	42, 44
Ph	Ph	<i>m</i> -Br	A	44
Ph	Ph	<i>m</i> -NO <sub>2</sub>	A	44
Ph	Ph	<i>p</i> -CN	A	44
Ph	Ph	<i>p</i> -NO <sub>2</sub>	A	44

<sup>a</sup> A, By heating at melting point; B, by refluxing with aqueous potassium hydroxide in ethanol; C, by refluxing with ammonium hydroxide in acetone; D, by refluxing with hydrochloric acid in ethanol.

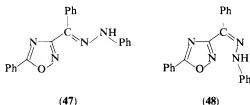
<sup>b</sup> The 4-amino-2,5-diphenyl-1,2,3-triazole was obtained.

Similar behavior was found for hydrazones and semicarbazones (45), which gave base-induced and also, in some cases thermally induced, rearrangements to 46.<sup>41</sup>

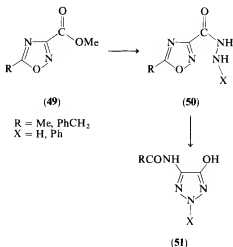




The geometric isomerism of phenylhydrazones has been studied in compound **43** ( $\text{Ar} = \text{R} = \text{Ph}$ ,  $\text{X} = \text{H}$ ).<sup>45,46</sup> 3-Benzoyl-5-phenyl-1,2,4-oxadiazole with phenylhydrazine in acetic acid at 20°C gave a mixture of *E*- (**47**) and *Z*- (**48**) isomers. Both isomers underwent thermal as well as base-induced rearrangement (piperidine in benzene): the *Z*-isomer rearranged directly, the *E*-isomer probably via intermediate *Z*-isomer formation (see Section III).



The hydrazide (**50**;  $\text{X} = \text{H}$ ), obtained from **49** and hydrazine, was also rearranged by heating or by the action of bases into 4-hydroxy-5-acylamino-1,2,3-triazole (**51**;  $\text{X} = \text{H}$ ).<sup>47</sup> Compound **49**, on heating with phenylhydrazine, gave **51** ( $\text{X} = \text{Ph}$ ) directly, clearly via a transient phenylhydrazide (**50**;  $\text{X} = \text{Ph}$ ), which underwent rapid conversion under the experimental conditions used.<sup>47</sup>



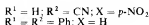
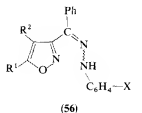
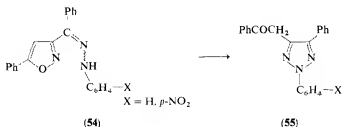
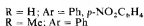
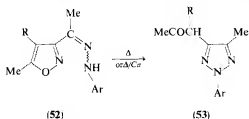
<sup>45</sup> N. Vivona, M. Ruccia, V. Frenna, and D. Spinelli, *J. Heterocycl. Chem.* **17**, 401 (1980).

<sup>46</sup> V. Frenna, N. Vivona, D. Spinelli, and G. Consiglio, *J. Heterocycl. Chem.* **17**, 861 (1980).

<sup>47</sup> M. Ruccia and N. Vivona, *Ann. Chim. (Rome)* **57**, 680 (1967).

## 2. Isoxazole

The arylhydrazones (52) of 3-acetylisoaxazoles rearranged to 53 by heating, with or without copper powder,<sup>2,48,49</sup> whereas the arylhydrazones of 3-benzoylisoaxazoles (54) rearranged to 55 on heating only in the presence of copper powder.<sup>43</sup> Compound 54 ( $X = p\text{-NO}_2$ ) also underwent a base-catalyzed rearrangement.<sup>43</sup> Arylhydrazones 56 did not rearrange.<sup>43,49</sup>



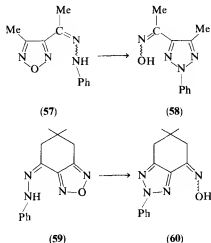
## 3. 1,2,5-Oxadiazole

Sodium salts derived from both geometric isomers of 3-acetyl-4-methyl-1,2,5-oxadiazole phenylhydrazone (57) rearranged in DMSO (140°C, 2 h)

<sup>48</sup> T. Ajello and S. Cusmano, *Gazz. Chim. Ital.* **70**, 770 (1940).

<sup>49</sup> T. Ajello and B. Tornetta, *Gazz. Chim. Ital.* **77**, 332 (1947).

to 4-acetyl-5-methyl-1,2,3-triazole oxime (**58**).<sup>2</sup> The alicyclic derivative **59** also rearranged to the 1,2,3-triazole **60**, but only under forcing conditions (potassium carbonate in DMSO, 120°C, 24 h) and in poor yield (25%),<sup>4</sup> indicating that such ring fusion does not accelerate the mhr, in contrast with the effect of benzo fusion.



### E. REARRANGEMENTS INVOLVING SEQUENCE XYZ = NCN: FINAL RING 1,2,4-TRIAZOLE

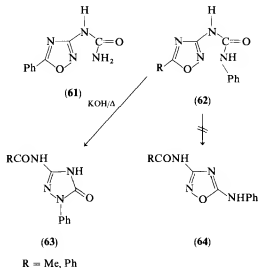
Literature data are available on the chemical reactivity of phenylureides and arylformamidines of 1,2,4-oxadiazole, isoxazole, and 1,2,5-oxadiazole. Careful choice of experimental conditions allows an interesting comparison between the reactivities of these three heterocycles in mhrs for the NCN side chain. The side chain could behave either as NCN or as NCO, but the rearrangements observed involved only the NCN sequence.

#### 1. 1,2,4-Oxadiazole

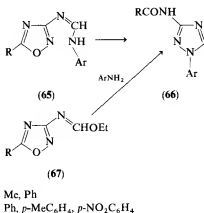
5-Phenyl-3-ureido-1,2,4-oxadiazole (**61**) did not rearrange on refluxing with sodium hydroxide in ethanol (only hydrolysis products were obtained).<sup>50</sup> 5-Substituted 3-phenylureido-1,2,4-oxadiazoles (**62**) were unaffected by melting; but on refluxing with aqueous potassium hydroxide in ethanol, rearrangement to 3-acyl amino-1,2,4-triazolin-5-ones (**63**) occurred,

<sup>50</sup> W. K. Warburton, *J. Chem. Soc. C*, 1522 (1966).

without any formation of 3-acylamino-5-anilino-1,2,4-oxadiazoles (**64**).<sup>51</sup> The difference in behavior of **61** and **62** can be attributed to the different acidity of the hydrogen at N'.



The more reactive 5-substituted 3-arylformamidino-1,2,4-oxadiazoles (**65**) were rearranged to 3-acylamino-1,2,4-triazoles (**66**) both by melting and by the action of sodium hydroxide in ethanol at 20°C. The same ring transformation is achieved by heating the 3-ethoxyformylamino-1,2,4-oxadiazoles (**67**) with anilines.<sup>52</sup>

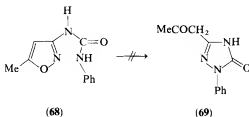


<sup>51</sup> M. Ruccia and N. Vivona, *Chem. Commun.*, 866 (1970).

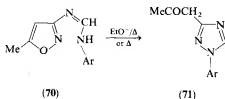
<sup>52</sup> M. Ruccia, N. Vivona, and G. Cusmano, *J. Heterocycl. Chem.*, **8**, 137 (1971).

## 2. Isoxazole

5-Methyl-3-phenylureidoisoxazole (**68**) did not rearrange to **69** either on melting or on refluxing with aqueous methanolic potassium hydroxide.<sup>2</sup>

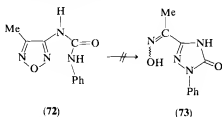


Here also, the arylformamidines were more reactive than the ureides: these compounds (**70**) were rearranged to 3-acetyl-1,2,4-triazoles (**71**) on melting or by refluxing with sodium ethoxide in ethanol.<sup>53</sup>



## 3. 1,2,5-Oxadiazole

3-Phenylurcido-4-methyl-1,2,5-oxadiazole (**72**) also did not rearrange to **73** on melting or by action of bases.<sup>54</sup>

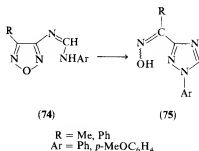


The previously described experimental conditions, which proved suitable to rearrange 1,2,4-oxadiazoles (see Section II.E,1) as well as isoxazoles (see Section II.E,2), failed in the case of the 4-substituted 3-arylformamidino-

<sup>53</sup> H. Kano and E. Yamazaki, *Tetrahedron* **20**, 159 (1964).

<sup>54</sup> M. Ruccia, N. Vivona, G. Cusmano, and G. Macaluso, *J. C. S. Perkin I*, 589 (1977).

1,2,5-oxadiazoles (**74**) (two geometric isomers were revealed by NMR). However, on heating with potassium *t*-butoxide in DMF at 130°C (6 h), **74** rearranged to oximes (**75**) of 3-acyl-1,2,4-triazoles either as the *E*-isomer alone or as both isomers as a function of the substituent, methyl or phenyl, present on C-4 of the starting ring.<sup>54</sup>



#### 4. General Considerations on the Influence of Structure of Both Starting Ring and Side Chain on Reactivity

It can be seen from the above results that, for a given side chain, the tendency to rearrange decreases, from 1,2,4-oxadiazole through isoxazole to 1,2,5-oxadiazole. This is determined by the electron structure of the starting ring (which affects the strength of the N—O bond that is cleaved in the rate-determining step), as well as the leaving-group capacity of ABO (which must accommodate the incipient negative charge in the transition state).

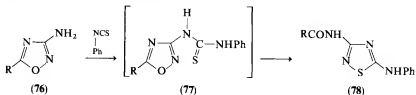
Moreover, for a given starting ring, the side-chain nature, or more particularly its nucleophilicity under the conditions employed, determines whether or not the rearrangement occurs. Thus, see, for example: (i) the effect of bases on the reactivity of ureido- (**61**) and phenylureido-1,2,4-oxadiazoles (**62**) and (ii) the behavior of phenylureido (**62**, **68**, **72**) and phenylformamidine (**65**, **70**, **74**) sequences.

#### F. REARRANGEMENTS INVOLVING SEQUENCE XYZ = NCS: FINAL RING 1,2,4-THIADIAZOLE

The only NCS side chain that has been studied in mhrs is that of some thioureides. Although in principle in this case the side chain is of both NCN and NCS type, in practice the rearrangements involve only the NCS sequence owing to the high nucleophilicity of the sulfur atom, which also results in the observed high reactivity.

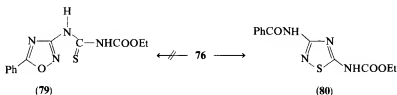
## 1. 1,2,4-Oxadiazole

Attempts<sup>55,56</sup> to synthesize 5-substituted 3-phenylthioureido-1,2,4-oxadiazoles (77) by reaction of 3-amino-1,2,4-oxadiazoles (76) with phenylisothiocyanate directly furnished 3-acylamino-5-anilino-1,2,4-thiadiazoles (78), the rearrangement products derived from 77 which underwent a fast mhr<sup>55,56</sup> under the experimental conditions.



R = Me, Ph

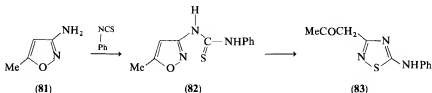
A literature report<sup>57</sup> indicated that 3-amino-5-phenyl-1,2,4-oxadiazole 76 (R = Ph) reacted with ethoxycarbonylisothiocyanate in refluxing ethyl acetate to give the stable thiourea 79. A reexamination<sup>30</sup> of this reaction showed that the product was the rearranged 1,2,4-thiadiazole 80 probably obtained through the intermediate formation of 79.



R = Ph

## 2. Isoxazole

3-Amino-5-methylisoxazole (81) with phenylisothiocyanate, under controlled experimental conditions, gave 3-phenylthioureido-5-methylisoxazole (82) which, in turn, rearranged to 3-acetonyl-5-phenylamino-1,2,4-thia-



<sup>55</sup> M. Ruccia, N. Vivona, and G. Cusmano, *J. C. S. Chem. Commun.*, 358 (1974).

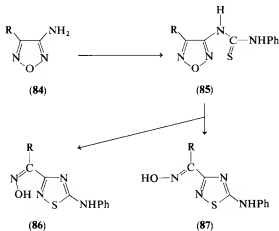
<sup>56</sup> N. Vivona, G. Cusmano, and G. Macaluso, *J. C. S. Perkin I*, 1616 (1977).

<sup>57</sup> G. Westphal and R. Schmidt, *Z. Chem.* **14**, 94 (1974) [*CA* **81**, 13445 (1974)].

diazole (**83**) on melting as well as in solution (very slowly in chloroform or in benzene, faster in protic or dipolar aprotic solvents) with or without a base.<sup>56</sup>

### 3. 1,2,5-Oxadiazole

The 4-substituted 3-phenylthioureido-1,2,5-oxadiazoles (**85**) were obtained from the corresponding amines (**84**) and phenylisothiocyanate.<sup>56</sup> At room temperature in the absence of bases **85** rearranged slowly, even in a dipolar aprotic solvent; in the presence of a base (aqueous potassium hydroxide in ethanol) they rearranged readily, giving the *Z*-oximes (**86**) of 3-acyl-5-anilino-1,2,4-thiadiazoles, i.e., products that conserved the geometry of the starting ring.<sup>56</sup> These reactions were also carried out under reflux, producing either the *E*-oxime (**87**) alone or a 1 : 1 mixture of **86** and **87** depending on the 4-substituent (methyl or phenyl)<sup>56</sup>. The oxime configurations were established from the products of their Beckmann rearrangement. Similar results were obtained in the heat-induced rearrangement.



R = Me, Ph

## G. REARRANGEMENTS INVOLVING SEQUENCE XYZ = NNN: FINAL RING TETRAZOLE

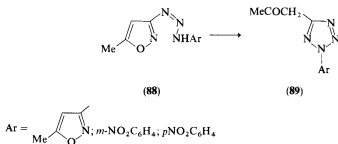
### 1. 1,2,4-Oxadiazole

No attempt has been made to bring about this ring conversion in 1,2,4-oxadiazole derivatives.



## 2. Isoxazole

The 3-diazoamino-5-methylisoxazole (**88**) readily rearranged in the presence of base to the 2-substituted 5-acetonilyltetrazole (**89**); two different mechanisms were proposed for this reaction<sup>58,59</sup>.



## 3. 1,2,5-Oxadiazole

An unsuccessful attempt to rearrange 3-aryldiazoamino-4-phenyl-1,2,5-oxadiazoles (**90**) has been reported.<sup>4</sup>



# H. REARRANGEMENTS INVOLVING SEQUENCE XYZ = NCC: FINAL RING IMIDAZOLE

## 1. 1,2,4-Oxadiazole

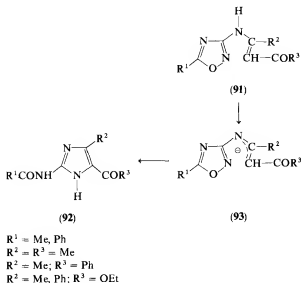
The 5-substituted 3-amino-1,2,4-oxadiazole (**76**) condensed with  $\beta$ -diketones and  $\beta$ -ketoesters, giving the corresponding 3-enaminones (**91**). These compounds did not rearrange on melting, but with sodium ethoxide in DMF (a dipolar aprotic solvent which increased the nucleophilic power of anion **93**) at 110°C they were converted into the 4-substituted 2-acylamino-5-acylimidazoles (**92**).<sup>60,61</sup>

<sup>58</sup> H. Kano and E. Yamazaki, *Chem. Pharm. Bull.* **10**, 993 (1962).

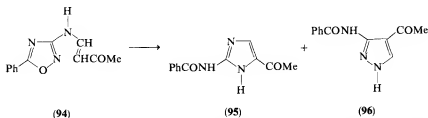
<sup>59</sup> H. Kano and E. Yamazaki, *Tetrahedron* **20**, 461 (1964).

<sup>60</sup> M. Ruccia, N. Vivona, and G. Cusmano, *Tetrahedron Lett.*, 4959 (1972).

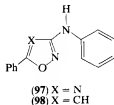
<sup>61</sup> M. Ruccia, N. Vivona, and G. Cusmano, *Tetrahedron* **30**, 3859 (1974).



The 3-enaminoketone **91** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{R}^3 = \text{Me}$ ) also rearranged to **92** with sodium hydride in DMF.<sup>62</sup> Compound **94**, however, was converted by sodium hydride in DMF to a mixture of the expected imidazole (**95**) and the pyrazole (**96**). This latter product, which is not formed by an mhr of the type under discussion, was proposed to arise through the intermediate formation of a diazirine and a carbodiimide.<sup>62</sup>



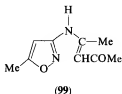
When the carbon atoms of the NCC sequence were part of an aromatic ring, as in 3-anilino-5-phenyl-1,2,4-oxadiazole (**97**), no rearrangement was observed.<sup>4</sup>



<sup>62</sup> M. Braun, G. Büchi, and D. F. Bushey, *J. Am. Chem. Soc.* **100**, 4209 (1978).

## 2. Isoxazole

Attempts to rearrange the enaminoketone (**99**)<sup>30</sup> and 3-anilino-5-methylisoxazole (**98**)<sup>4</sup> to the corresponding imidazoles failed.



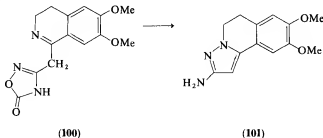
## 3. 1,2,5-Oxadiazole

No attempt to bring about this ring conversion has been reported in the 1,2,5-oxadiazole series.

### I. REARRANGEMENTS INVOLVING SEQUENCE XYZ = CCN: FINAL RING PYRAZOLE

#### 1. 1,2,4-Oxadiazole

The 1,2,4-oxadiazolin-5-one (**100**) was converted into the fused pyrazole (**101**) by heating at 180–200°C, followed by treatment with dilute hydrochloric acid.<sup>63</sup>

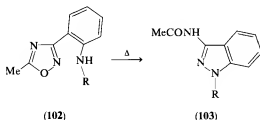


Also, the 3-(*o*-aminophenyl)- and 3-(*o*-methylaminophenyl)-5-methyl-1,2,4-oxadiazoles (**102**; R = H, Me) rearranged under forcing conditions (long heating at 160–180°C) to 3-acetaminoindazoles (**103**).<sup>64</sup> Because of the

<sup>63</sup> K. Takács, L. Szekers, K. Harsányi, G. Papp, A. Meszmelyi, and E. Benedek, *Ger. Offen.* 2,332,860 (1974) [*CA* **80**, 133434 (1974)].

<sup>64</sup> N. Vivona, G. Cusmano, G. Macaluso, V. Frenna, and M. Ruccia, *J. Heterocycl. Chem.* **16**, 783 (1979); see also D. Korbonits and P. Kiss, *Seventh International Congress of Heterocyclic Chemistry*, Tampa, Florida, August 12–17, 1979, p. 170.

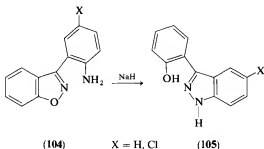
very low acidity of the hydrogen atom on the nitrogen of the CCN sequence, the base-catalyzed rearrangement was not observed. In contrast, the acetyl derivative (**102**;  $R = \text{COCH}_3$ ) did not rearrange even on long heating at  $180^\circ\text{C}$ ; but with potassium hydroxide, it underwent a base-induced conversion to **103** ( $R = \text{H}$ ).<sup>64</sup>



A rearrangement involving a saturated CCN side chain has been reported<sup>65,66</sup> and will be discussed in Section III.

## 2. Isoxazole

The 3-(*o*-aminoaryl)benzoisoxazoles (**104**) rearrange on refluxing in the presence of sodium hydride (or  $\text{LiAlH}_4$ ) in THF to 5-substituted 3-(*o*-hydroxyphenyl)indazoles (**105**).<sup>67</sup>



## 3. 1,2,5-Oxadiazole

No attempt to realize this ring conversion has been reported in 1,2,5-oxadiazole derivatives.

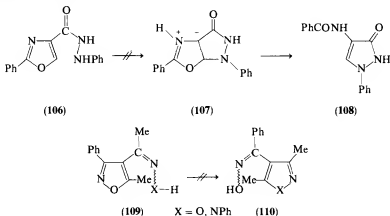
<sup>65</sup> D. Korbonits, K. Harsányi, E. Molnár, K. Takács, G. Hēja, J. Bodnár, I. Bodrogi, and J. Erödi, Ger. Offen. 2,038,919 (1971) [*CA* **74**, 112039 (1971)].

<sup>66</sup> D. Korbonits, E. M. Bakó, and K. Horvath, *J. Chem. Res. (S)*, 64 (1979).

<sup>67</sup> A. Walser, T. Flynn, and R. I. Fryer, *J. Heterocycl. Chem.* **11**, 885 (1974).

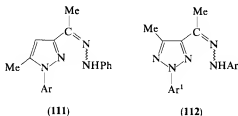
### III. Miscellaneous

There are reports of many attempts to induce rearrangements in which the reaction center of the starting ring is an atom other than nitrogen. When the reaction center is a carbon atom (see **106**<sup>6</sup> and **109**<sup>68</sup>) under typical mhr conditions (heat-induced or base-induced) they failed. For ring interconversions with sulfur instead of nitrogen see references cited in Ref. 4.



It is well known that, in the presence of acids<sup>69</sup> or under the conditions of Wolff-Kishner reduction,<sup>70</sup> some azole derivatives undergo ring conversions, but these cannot be classified as mhrs.

Attempts to bring about rearrangements in rings in which fission of an N—N bond instead of an N—O bond would be required failed in all cases; therefore, compounds **111** and **112** did not rearrange.<sup>4</sup> This type of ring conversion does not occur even in benzo-fused derivatives, which are known to undergo rearrangements more easily than those in the monocyclic series.<sup>4,71</sup>



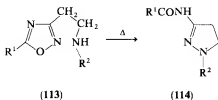
<sup>68</sup> A. Padwa, E. Chen, and A. Ku, *J. Am. Chem. Soc.* **97**, 6484 (1975).

<sup>69</sup> V. Dave and E. W. Warnhoff, *Can. J. Chem.* **54**, 1022 (1976).

<sup>70</sup> H. C. van der Plas, "Ring Transformations of Heterocycles," Vol. I, p. 207, and references therein. Academic Press, New York, 1973.

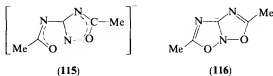
<sup>71</sup> H. Balli and S. Gunzenhauser, *Helv. Chim. Acta* **61**, 2628 (1978).

An interesting example of the synthesis of a pyrazoline via ring interconversion involving a saturated side chain has been studied in detail (113  $\rightarrow$  114).<sup>65,66</sup> This reaction is unlike the classical mhrrs: in this case, the starting ring and side chain do not form a continuous  $\pi$ -electron system, and the conversion is azole-to-azoline and not azole-to-azole, as in the original scheme 1  $\rightarrow$  2.

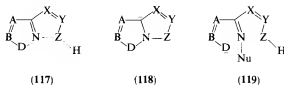


#### IV. Mechanism of Mononuclear Heterocyclic Rearrangements

Ruccia *et al.*<sup>35</sup> studied the degenerate rearrangement of the potassium salt of 3-acetylamino-5-methyl-1,2,4-oxadiazole (29). They suggested the possible formation of a symmetrical anion as transition state (115) or intermediate (116).



Soon there after, Katritzky *et al.*<sup>6</sup> suggested that mhrrs could, in principle, proceed via three distinct routes which involve, respectively (i) a cyclic concerted transition state (117), (ii) a bicyclic intermediate (118), and (iii) an acyclic intermediate (119).



Around this time, Spinelli *et al.*<sup>72</sup> commenced research into the mechanism of mhrrs using as substrates the arylhydrazones of 5-substituted 3-benzoyl-1,2,4-oxadiazoles (43) which rearranged to the 2-aryl-5-phenyl-4-acylamino-

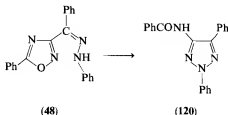
<sup>72</sup> D. Spinelli, A. Corrao, V. Frenna, N. Vivona, M. Ruccia, and G. Cusmano, *J. Heterocycl. Chem.* **13**, 357 (1976).

1,2,3-triazoles (44). The compounds studied most extensively were the phenylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole. The rearrangement of the *Z*-isomer (48) was investigated in dioxane/water in the presence of various buffers and in benzene in the presence of piperidine. The behavior of the *E*-isomer (47) was investigated only in benzene.

#### A. REARRANGEMENT OF ARYLHYDRAZONES (*Z*-ISOMERS) OF 3-BENZOYL-5-PHENYL-1,2,4-OXADIAZOLE IN DIOXANE/WATER

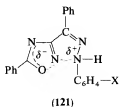
The data obtained can be summarized as follows:

1. At  $pS^+ \geq 3.8$ , compound 48 rearranged to 120. At lower  $pS^+$  it also underwent hydrolysis to 3-benzoyl-5-phenyl-1,2,4-oxadiazole and phenylhydrazine.



2. In the range of  $pS^+ 3.8$ – $6.8$ , the rate of reaction was  $pS^+$ -independent; at higher  $pS^+$ , it increased sharply with increasing  $pS^+$ . This indicates the occurrence of two different reactions, the second being base-catalyzed. The rate constant values in the base-catalyzed range were affected by the nature of the buffer used, indicating that general base catalysis operates.

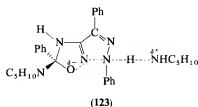
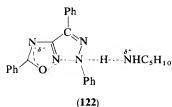
3. The effects of substituents in the arylhydrazone moiety were studied in the  $pS^+$ -independent range<sup>44</sup>. Data at  $pS^+ 3.80$  were correlated by means of the Ingold–Yukawa–Tsuno equation ( $\rho -1.31$ ,  $r^+ 0.10$ ,  $r^- 0.25$ ). The low susceptibility constants observed were attributed to a balancing between opposite electronic effects by substituents in the stages preceding the rate-determining step, according to a transition state of the  $S_Ni$  type (structure 121).



4. On the other hand, an examination of substituent effects in the whole range of  $pS^+$  3.8–11.5 shows that both strong electron-repelling and electron-withdrawing substituents accelerate the rearrangement, indicating a non-linear, concave upward Hammett plot in the base-catalyzed range.<sup>73</sup>

#### B. REARRANGEMENT AND ISOMERIZATION OF PHENYLHYDRAZONE (*E*- AND *Z*-ISOMERS) OF 3-BENZOYL-5-PHENYL-1,2,4-OXADIAZOLE IN BENZENE

A kinetic study in benzene in the presence of piperidine indicated that **48** rearranged directly to **120**, whereas **47** first underwent isomerization to **48**, which then rearranged. The rearrangement of **48** required piperidine catalysis (the uncatalyzed reaction was very slow): two catalyzed pathways occur involving, respectively, one and two molecules of piperidine. Transition state **122** was suggested for the second-order and **123** for the third-order reaction.<sup>46</sup>



The addition of a piperidine molecule at the  $C_5-N_4$  bond of 1,2,4-oxadiazole ring favored the progress of the reaction. This type of addition is similar to the hypothesis of Harsanyi for the rearrangement of other 1,2,4-oxadiazole derivatives.<sup>39</sup>

The isomerization of the *E*-isomer (**47**) to the *Z*-isomer (**48**) was wholly piperidine-catalyzed (one molecule) and proceeded through the usual addition-elimination mechanism.<sup>74</sup>

#### ACKNOWLEDGMENTS

The authors are indebted to Professor A. R. Katritzky and Doctor A. J. Boulton for their criticism.

<sup>73</sup> D. Spinelli, V. Frenna, A. Corrao, N. Vivona, and M. Ruccia, *J. Heterocycl. Chem.* **16**, 359 (1979).

<sup>74</sup> A. J. Bellamy and J. Hunter, *J. C. S. Perkin I*, 456 (1976); P. R. Conlon and J. M. Sayer, *J. Org. Chem.* **44**, 262 (1979), and references therein.



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# Recent Advances in the Chemistry of Benzo[*b*]thiophenes

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## I. Introduction

The chemistry of benzo[*b*]thiophene has previously been reviewed by Hartough and Meisel (to 1952)<sup>1</sup> and by Iddon and Scrowston (1952–1968).<sup>2</sup> The present review covers the period July 1978 to June 1980. Last time we

proudly claimed to have covered all publications coming within the scope of the review. It is now impossible to give exhaustive coverage of well over a thousand new references. As before, biologically active benzo[b]thiophenes have been largely excluded since they have been excellently reviewed by Campaigne *et al.*<sup>3,4</sup> The sections on benzo[b]thiophenes from petroleum and coal tar have now been deleted; the latter topic has been reviewed elsewhere.<sup>5</sup> Methods for the ring synthesis of benzo[b]thiophenes have been admirably reviewed by Dr. B. Iddon,<sup>6</sup> and there is now no specific section on the subject. More important synthetic developments have been included as appropriate in Section IV. Otherwise, apart from additional sections reflecting current trends in benzo[b]thiophene chemistry, the general pattern of the review follows that used previously.<sup>2</sup>

Until a decade or so ago, the basic chemistry of benzo[b]thiophene was being explored: general synthetic methods were being investigated and means were being found for the routine introduction of functionality into the molecule. Now, however, its chemistry has become infected with the air of sophistication which pervades the whole of organic chemistry. In particular, the molecule is being used as a convenient model for investigating the role played by the sulfur atom in heteroaromatic sulfur compounds in general. There has been considerable interest in photochemical and cycloaddition reactions, in ring expansion and ring fission, and in the study of benzo[b]thiophenium salts and *S*-oxides. Much of the work has been supported by molecular orbital (MO) calculations of increasing complexity and by application of more refined spectroscopic techniques. At the other end of the spectrum, it is sad that a good deal of highly fragmented, routine work is being published—often almost identically in different journals, and often without mention of similar work reported previously by others.

Much of the current interest in benzo[b]thiophene chemistry owes its origins to the wide range of biological and other activities shown by many of its derivatives. In medicine, benzo[b]thiophene derivatives have been patented as laxatives,<sup>7</sup> contraceptives,<sup>8</sup> and antiinfluenza agents.<sup>9</sup> In

<sup>1</sup> H. D. Hartough and S. L. Meisel, in "Compounds with Condensed Thiophene Rings" (A. Weissberger, ed.), Chapter II. Wiley (Interscience), New York, 1954.

<sup>2</sup> B. Iddon and R. M. Scowston, *Adv. Heterocycl. Chem.* **11**, 177 (1970).

<sup>3</sup> T. R. Bosin and E. E. Campaigne, *Adv. Drug Res.* **11**, 191 (1977).

<sup>4</sup> E. Campaigne, D. R. Knapp, E. S. Neiss, and T. R. Bosin, *Adv. Drug Res.* **5**, 1 (1970).

<sup>5</sup> J. Vymetal, *Chem. Listy* **62**, 1439 (1968).

<sup>6</sup> B. Iddon, *Stud. Org. Chem. (Amsterdam)* **3** (New Trends Heterocycl. Chem.), 250 (1979).

<sup>7</sup> R. J. Meyer, O. E. Horsley, and H. J. Eichel, U.S. Patent 3,676,559 (1972) [CA **77**, 114238 (1972)].

<sup>8</sup> C. D. Jones and T. Suarez, Ger. Offen. 2,647,864 (1977) [CA **87**, 102155 (1977)].

<sup>9</sup> J. E. Boyd and R. G. Sommerville, *Arch. Gesamte Virusforsch.* **46**, 78 (1974) [CA **82**, 92948 (1975)].

agriculture, some are active as fungicides,<sup>10</sup> pesticides,<sup>11</sup> and herbicides,<sup>12</sup> while others have more specific uses in preventing slime formation in water<sup>13</sup> and in aiding the ripening of sugar cane.<sup>14</sup> As veterinary products, some benzo[b]thiophene derivatives promote the growth of animals<sup>15</sup> and the growth of wool on lambs,<sup>16</sup> whereas prostaglandin analogs act as contraceptives in pigs and cows.<sup>17</sup> Other derivatives may be used as fluorescent whiteners,<sup>18</sup> as moth-proofing agents,<sup>19</sup> as the basis of polymers,<sup>20</sup> and as additives prior to the dyeing of human hair.<sup>21</sup> 3-Benzo[b]thenoyltrifluoroacetone has many uses in analytical chemistry, including the colorimetric determination of several transition-metal ions.<sup>22</sup>

Benzo[b]thiophenes have been found in unexpected places: in cooked potato peel,<sup>23</sup> as volatile constituents of white bread crust,<sup>24</sup> in off-flavored unblanched green peas,<sup>25</sup> in eels which have been exposed to seawater containing crude oil,<sup>26</sup> and as components of automobile exhaust soot.<sup>27</sup>

New and efficient catalytic processes for preparing benzo[b]thiophene from readily available starting materials, e.g., phenylacetaldehyde,<sup>28</sup> ethylbenzene,<sup>29</sup> and styrene,<sup>30</sup> have been announced. It is a pity, therefore, that it is so expensive (approximately \$1 per gram). Cost is likely to be a critical factor controlling future research output.

<sup>10</sup> T. Akita, F. Araki, H. Kurono, and T. Harada, Japan. Kokai 76/118,835 (1976) [CA 86, 66846 (1977)].

<sup>11</sup> L. S. Fuller, J. W. Pratt, and F. S. Yates, *Manuf. Chem. & Aerosol News* 49, 58 (1978).

<sup>12</sup> P. R. Driscoll and H. A. Kaufman, U.S. Patent 3,495,967 (1970) [CA 72, 90268 (1970)].

<sup>13</sup> A. Saito, T. Sugi, and A. Maeda, Japan. Kokai 76/148,018 (1976) [CA 86, 151495 (1977)].

<sup>14</sup> J. V. Karabinos and L. G. Nickell, Ger. Offen. 2,627,935 (1977) [CA 86, 139839 (1977)].

<sup>15</sup> G. Asato, Ger. Offen. 2,501,788 (1975) [CA 84, 59176 (1976)].

<sup>16</sup> J. M. Pensack, Braz. Pedido PI 78/02,533 (1978) [CA 91, 814 (1979)].

<sup>17</sup> I. C. I. Ltd., Fr. Demande 2,215,961 (1974) [CA 82, 139492 (1975)].

<sup>18</sup> N. N. Crounse and K. B. Desai, U.S. Patent 3,932,301 (1976) [CA 84, 123423 (1976)].

<sup>19</sup> O. Johansen, W. H. F. Sasse, R. M. Hoskinson, and I. M. Russell, *J. Text. Inst.* 67, 146 (1976).

<sup>20</sup> M. Ueda, Y. Miyazawa, A. Sato, and Y. Imai, *Polym. J.* 8, 609 (1976).

<sup>21</sup> K. J. Boosen, P. Berth, and G. Reese, U.S. Patent 3,482,923 (1969) [CA 77, 92737 (1972)].

<sup>22</sup> J. R. Johnston and W. J. Holland, *Mikrochim. Acta*, 321 (1972), and previous papers in the series.

<sup>23</sup> D. F. Meigh, A. A. Filmer, and R. Self, *Phytochemistry* 12, 987 (1973).

<sup>24</sup> D. J. Folkes and J. W. Gramshaw, *J. Food Technol.* 12, 1 (1977).

<sup>25</sup> K. E. Murray, J. Shipton, F. B. Whitfield, and J. H. Last, *J. Sci. Food Agric.* 27, 1093 (1976).

<sup>26</sup> M. Ogata and Y. Miyake, *Proc. Jpn. Acad., Ser. B* 54, 423 (1978) [CA 89, 21008 (1978)].

<sup>27</sup> J. B. F. Lloyd, *J. Forensic Sci. Soc.* 11, 235 (1971).

<sup>28</sup> J. Barrault, M. Guisnet, J. Lucien, and R. Maurel, *J. Chem. Res. (S)*, 207 (1978).

<sup>29</sup> V. P. Litvinov and E. G. Ostapenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1683 (1971) [CA 75, 151705 (1971)].

<sup>30</sup> V. N. Kulakov, M. F. Pankratova, and Yu. M. Pinegina, *Khim. Seraorg. Soedin., Soderzh. Neftnykh Nefteprod.* 9, 25 (1972) [CA 82, 72701 (1975)].

## II. Molecular Structure and Physical Properties of Benzo[b]thiophenes

### A. MOLECULAR ORBITAL TREATMENT

The application of MO calculations to sulfur heterocycles in general is beset with problems<sup>31</sup>; in our last review we showed that the earliest attempts to apply Hückel MO (HMO) calculations to benzo[b]thiophene had met with little success.<sup>2</sup> Numerous workers have since taken up the challenge to obtain meaningful results. The majority have performed semiempirical calculations on benzo[b]thiophene within the  $\pi$ -approximation, using either the Hückel<sup>32-36</sup> or the self-consistent field (SCF) scheme.<sup>36-47</sup> Configuration interaction has been added in two cases.<sup>48,49</sup> All-valence electron calculations have also been reported, both of the semiempirical SCF type, using the CNDO approximation,<sup>33,38,47</sup> and of the *ab initio* SCF type.<sup>50,51</sup> The *d*-orbitals of the sulfur atom were included in the all-valence electron calculations, but excluded in many of the others. Calculations are based on an assumed geometry and are therefore immediately subject to limitations.

Attempts have been made to calculate electronic transition energies,<sup>39-43,45,46,48,49</sup> dipole moment,<sup>39,47,49,50</sup> orbital energies or ionization

<sup>31</sup> R. Zahradnik, *Adv. Heterocycl. Chem.*, **5**, 1 (1965).

<sup>32</sup> H. Güston, L. Klasinc, and B. Ruscic, *Z. Naturforsch., Teil A* **31**, 1051 (1976).

<sup>33</sup> C. Guimon, M. F. Guimon, G. Pfister-Guillouzo, P. Geneste, J. L. Olivé, and S. N. Ung, *Phosphorus Sulfur* **5**, 341 (1979).

<sup>34</sup> I. Gutman, M. Milun, and N. Trinajstić, *J. Am. Chem. Soc.*, **99**, 1692 (1977).

<sup>35</sup> B. A. Hess and L. J. Schaad, *J. Am. Chem. Soc.*, **95**, 3907 (1973).

<sup>36</sup> P. A. Clark, R. Gleiter, and E. Heilbronner, *Tetrahedron* **29**, 3085 (1973).

<sup>37</sup> M. J. S. Dewar and N. Trinajstić, *J. Am. Chem. Soc.*, **92**, 1453 (1970).

<sup>38</sup> A. Helland and P. N. Skancke, *Acta Chem. Scand.*, **26**, 2601 (1972).

<sup>39</sup> A. Skancke and P. N. Skancke, *Acta Chem. Scand.*, **24**, 23 (1970).

<sup>40</sup> R. A. W. Johnstone and S. D. Ward, *Tetrahedron* **25**, 5485 (1969).

<sup>41</sup> Z. Yoshida and T. Kobayashi, *Theor. Chim. Acta* **20**, 216 (1971).

<sup>42</sup> F. P. Billingsley and J. E. Bloor, *Theor. Chim. Acta* **11**, 325 (1968).

<sup>43</sup> J. Fabian, A. Mehlhorn, and R. Zahradnik, *Theor. Chim. Acta* **12**, 247 (1968).

<sup>44</sup> E. Corradi, P. Lazzeretti, and F. Taddei, *Mol. Phys.*, **26**, 41 (1973).

<sup>45</sup> J. Fabian, *Z. Phys. Chem. (Leipzig)* **260**, 81 (1979).

<sup>46</sup> L. Klasinc, E. Pop, N. Trinajstić, and J. V. Knop, *Tetrahedron* **28**, 3465 (1972).

<sup>47</sup> R. A. W. Johnstone and F. A. Mellon, *J. C. S., Faraday 2* **69**, 1155 (1973).

<sup>48</sup> L. Klasinc and J. V. Knop, *Z. Naturforsch., Teil B* **26**, 1235 (1971).

<sup>49</sup> J. Fabian, A. Mehlhorn, and R. Zahradnik, *J. Phys. Chem.*, **72**, 3975 (1968).

<sup>50</sup> M. H. Palmer and S. M. F. Kennedy, *J. C. S. Perkin II*, 1893 (1974).

<sup>51</sup> M. H. Palmer and S. M. F. Kennedy, *J. C. S. Perkin II*, 81 (1976).

potentials,<sup>32,33,36,37,40-42,47,49,50,52</sup>  $\pi$ -electron densities,<sup>37,46</sup> bond orders,<sup>46</sup> bond lengths,<sup>37,39</sup> free valence indices,<sup>38,46</sup> various reactivity indices,<sup>38</sup> heat of atomization,<sup>37</sup> and <sup>1</sup>H chemical shifts.<sup>44</sup> Although authors tend to describe their results as being "as good as can be expected," or "satisfactory," or even in some cases as "excellent," the fact remains that they are generally disappointing, at least in cases where comparison with experimental observations is possible.

Attempts to compare the aromatic character of benzo[*b*]thiophene with that of related molecules have been more successful. Thus, the calculated resonance energy is in excess of that of thiophene<sup>35</sup> or benzene.<sup>37</sup> The topological resonance energy, which is directly related to the topology of the molecular  $\pi$ -network, has been calculated.<sup>34</sup> Palmer's *ab initio* results show that the calculated resonance energy of 242 kJ mol<sup>-1</sup>, based on a *sp*-model for benzo[*b*]thiophene, is increased by 41 kJ mol<sup>-1</sup> when *d*-orbitals are taken into consideration.<sup>50</sup> A study of resonance energies and of the distributions of the  $\pi$ -electrons establishes the following sequence of aromatic character: naphthalene > benzo[*b*]thiophene = indole > benzo[*b*]furan.<sup>50</sup> Benzo[*c*]thiophene has a lower resonance energy and a lower triplet state than the [*b*]-isomer, and has therefore lower aromatic character.<sup>51</sup> The delocalization of the  $\pi$ -electrons has been investigated by configuration analysis of the state functions of the heterocycle<sup>45</sup> and the ring current effect has been calculated.<sup>44</sup>

Molecular orbital calculations have given some insight into the role of the sulfur 3*d*-orbitals. *Ab initio* calculations suggest that they act as polarization functions, rather than as strongly bonding orbitals;<sup>50</sup> CNDO/2 calculations indicate that the involvement of the 3*d* $\pi$ -orbitals in sulfur heterocycles increases as the degree of donation of the 3*p* $\pi$ -electrons increases.<sup>47</sup> The first three bands in the UV photoelectron (PE) spectrum of benzo[*b*]thiophene have been assigned to  $\pi$ -ionization potentials on the basis of band shapes and MO calculations.<sup>32,33,36,47,50,52</sup> A comparison of calculated and measured ionization potentials suggests that 3*d*-orbital participation must be very small.<sup>36</sup> On the other hand, the striking resemblance of the PE spectrum to that of the iso- $\pi$ -electronic hydrocarbons, naphthalene and anthracene, has been explained by use of 3*d*-orbitals, and it has been shown that substitution of a C=C double bond in a conjugated system by a sulfur atom does not greatly affect the orbital energies.<sup>47</sup>

Molecular orbital calculations have also been applied to benzo[*b*]thiophene derivatives. Predictably, the results are usually less satisfactory than those for the parent molecule. However, the interaction of the sulfone group

<sup>52</sup> J. H. D. Eland, *Int. J. Mass Spectrom. Ion Phys.* **2**, 471 (1969).

in benzo[b]thiophene 1,1-dioxide with the 2,3-double bond has been examined by the HMO method, and the energy of the longest wavelength absorption band has been related to the calculated  $N \rightarrow V_1$  transition energy.<sup>53</sup> The UV spectra of 2,3-dihydrobenzo[b]thiophene and its 3-oxo derivative have been assigned on the basis of molecules-in-molecules (MIM) calculations.<sup>54</sup> Galasso *et al.* have used CNDO and INDO methods on benzo[b]thiophene-2,3-dione to calculate the dipole moment<sup>55</sup> and examine features of the UV,<sup>56</sup>  $^1\text{H-NMR}$ ,<sup>57</sup>  $^{13}\text{C-NMR}$ ,<sup>58</sup> and PE spectra.<sup>59</sup> The authors admit in one case that the calculations "do not give an overall accurate reproduction of the spectral patterns."<sup>58</sup> Russian workers have used a modified Pariser-Parr-Pople method to calculate the electronic spectrum of **1** ( $X = \text{O}$ ,  $Y = \text{CHPh}$ )<sup>60</sup> and confirm the experimental observation that **1** ( $X = \text{O}$  or  $\text{S}$ ,  $Y = \text{CHNHR}$ ) exist as shown as the (thi)oxo tautomers.<sup>61</sup>



(I)

The barriers to pyramidal inversion in the *S*-methyl derivative and *S*-oxide of 2-methylbenzo[b]thiophene have been calculated (CNDO/2); the value of the former is in good agreement with that obtained by an NMR method.<sup>62</sup>

For benzo[b]thiophene and related molecules, attempts have been made to correlate experimentally determined partition coefficients with calculated (HMO) values of superdelocalizability and charge density, in the hope of applying MO theory to studies of biological activity.<sup>63,64</sup>

<sup>53</sup> F. de Jong and M. Janssen, *J. C. S. Perkin II*, 572 (1972).

<sup>54</sup> G. Kresze and W. Amann, *Spectrochim. Acta, Part A* **24**, 1283 (1968).

<sup>55</sup> V. Galasso and G. C. Pappalardo, *J. C. S. Perkin II*, 574 (1976).

<sup>56</sup> V. Galasso, *Gazz. Chim. Ital.* **106**, 571 (1976).

<sup>57</sup> V. Galasso, G. Pellizer, A. Lisini, and A. Bigotto, *Org. Magn. Reson.* **7**, 591 (1975).

<sup>58</sup> V. Galasso, G. Pellizer, and G. C. Pappalardo, *Org. Magn. Reson.* **9**, 401 (1977).

<sup>59</sup> V. Galasso, F. P. Colonna, and G. Distefano, *J. Electron Spectrosc. Relat. Phenom.* **10**, 227 (1977).

<sup>60</sup> M. A. Mostoslavskii and G. A. Yugai, *Ukr. Khim. Zh. (Russ. Ed.)* **42**, 1219 (1976) [*CA* **86**, 105253 (1977)].

<sup>61</sup> V. I. Minkin, V. A. Kosobutskii, B. Ya. Simkin, and Yu. A. Zhdanov, *J. Mol. Struct.* **24**, 237 (1975).

<sup>62</sup> J. D. Andose, A. Rauk, R. Tang, and K. Mislow, *Int. J. Sulfur Chem., Part A* **1**, 66 (1971).

<sup>63</sup> K. S. Rogers and A. Cammarata, *J. Med. Chem.* **12**, 692 (1969).

<sup>64</sup> K. S. Rogers and A. Cammarata, *Biochim. Biophys. Acta* **193**, 22 (1969).



Many workers have tried to predict the site of electrophilic substitution in benzo[*b*]thiophene derivatives with the aid of calculated electron densities, but have met with only limited success. Epiotis *et al.*<sup>65</sup> have considered electrophilic substitution from the HOMO/LUMO standpoint, and have used a simple Hückel-type model for 5-membered heterocycles to relate the shift in the position of electrophilic attack in going from benzo[*b*]furan to benzo[*b*]thiophene to the smaller energy gap between the two higher filled  $\pi$ -orbitals in thiophene as compared with furan. Having refined this treatment, other workers obtained a qualitative correlation between the nucleophilic reactivity of benzo[*b*]thiophene and some of its derivatives and the energies (and localization) of frontier orbitals.<sup>33</sup> The present state of many MO calculations, as applied to derivatives of benzo[*b*]thiophene, may be illustrated by reference to a study of the acylation of methyl benzo[*b*]thiophene-3-carboxylate.<sup>66</sup> Simple HMO calculations failed to predict the position of substitution, but after a profound frontier orbital treatment the authors were able to conclude that "with a stronger electron-withdrawing group attached to benzo[*b*]thiophene, the resulting compound will show a lower reactivity towards electrophilic substitution"!

## B. SPECTROSCOPY

### 1. NMR Spectra

a. <sup>1</sup>H NMR. Proton NMR spectroscopy is unsurpassed as a tool for routine structure determination in benzo[*b*]thiophene chemistry, and many elegant examples of its applications will become evident in the ensuing sections. Full iterative analyses of the complex spectrum of the parent benzo[*b*]thiophene in various solvents have been carried out.<sup>67-69</sup> All chemical shifts and coupling constants, including small inter-ring couplings, have been assigned. In terms of partial bond fixation, the  $J_{ortho}$  coupling constants suggest that the aromaticity of benzo[*b*]thiophene is comparable with that of naphthalene.<sup>68</sup> Chemical shifts in benzo[*b*]thiophene and other condensed thiophenes have been considered in terms of the  $\pi$ -electron density variations to be expected from different models for the bonding of sulfur.<sup>70</sup>

<sup>65</sup> N. D. Epiotis, W. R. Cherry, F. Bernardi, and W. J. Hehre, *J. Am. Chem. Soc.* **98**, 4361 (1976).

<sup>66</sup> M. Hannoun, N. Blazevic, D. Kolbah, A. Sabljic, N. Trinajstic, A. Sega, A. Lisini, F. Kajfez, and V. Sunjic, *J. Heterocycl. Chem.* **16**, 1029 (1979).

<sup>67</sup> D. F. Ewing and R. M. Scrowston, *Org. Magn. Reson.* **3**, 405 (1971).

<sup>68</sup> K. D. Bartle, D. W. Jones, and R. S. Matthews, *Tetrahedron* **27**, 5177 (1971).

<sup>69</sup> F. Balkau and M. L. Heffernan, *Aust. J. Chem.* **25**, 327 (1972).

<sup>70</sup> P. M. Nair and V. N. Gogte, *Indian J. Chem.* **12**, 589 (1974).

From such a study, it appears that the sulfur atom acts as a  $\pi$ -donor. The spectrum of benzo[*b*]thiophene in a nematic solvent is consistent with a planar molecule without significant distortion in the geometry of the benzene and thiophene rings.<sup>71</sup>

The effects of substituents on chemical shifts have been widely studied. The deshielding effect of an acetyl group depends on the location of the group and can be used to identify isomeric acetylbenzo[*b*]thiophenes.<sup>72</sup> A 3-methyl group causes shielding of H-4, as does an alicyclic ring fused across the 2,3-positions. However, a 3-sulfur substituent (either SMe or part of a reduced sulfur-carbon ring) does not have much effect on H-4.<sup>73</sup> A 3-*t*-butyl group causes deshielding of H-4.<sup>74</sup> The magnitude of the deshielding of ring protons accompanying acetylation of a primary amine is related to the preferred conformation of the amide.<sup>75</sup> The variations in chemical shift of H-4 and H-6 brought about by changing the 5-substituent have been correlated with the extended Hammett equation, either in its original form or with a modification to include steric effects.<sup>76</sup>

Studies in solution suggest specific association of chloroform with the benzo[*b*]thiophene molecule and interaction of acetone with the sulfur atom.<sup>67</sup> Complexation constants of benzo[*b*]thiophene with polar solvents (e.g., DMF, 2-pyrrolidone) have been determined by an NMR method.<sup>77</sup> In the complex of benzo[*b*]thiophene with  $\text{Ag}^+$ , the metal ion is strongly associated with the lone pair of electrons on the sulfur atom<sup>78</sup>; in the 1,3,5-trinitrobenzene complex, NMR data suggest that the trinitro compound lies over the phenyl ring of the heterocycle.<sup>78,79</sup> Likewise, in the chromium tricarbonyl complex, the  $\text{Cr}(\text{CO})_3$  group is bonded to the benzenoid ring.<sup>80</sup> Studies of the structure of benzo[*b*]thiophenium salts will be discussed in Section III,A,2.

Thioindoxyl exists mainly as the oxo tautomer (71%) in DMSO.<sup>81</sup> Introduction of a 2-methyl group increases the degree of enolization (in  $\text{CCl}_4$  or

<sup>71</sup> C. L. Khetrapal, A. C. Kunwar, and A. Saupe, *Liq. Cryst., Proc. Int. Conf.*, 1973, 495 (1975).

<sup>72</sup> P. Faller, *Bull. Soc. Chim. Fr.*, 934 (1969).

<sup>73</sup> D. Cagniant, P. Cagniant, and J. Trierweiler, *Bull. Soc. Chim. Fr.*, 601 (1969).

<sup>74</sup> J. Cooper and R. M. Scowston, *J. C. S. Perkin I*, 414 (1972).

<sup>75</sup> R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rac, *Can. J. Chem.* **46**, 2577 (1968).

<sup>76</sup> M. Charton, *J. Org. Chem.* **36**, 266 (1971).

<sup>77</sup> V. G. Podolyak, E. P. Prokof'ev, M. I. Zaretskii, S. Z. Taitis, I. V. Usyshkina, and V. B. Golub, *Zh. Obshch. Khim.* **49**, 1609 (1979) [*CA* **92**, 41067 (1980)].

<sup>78</sup> K. K. Deb, T. C. Cole, and J. E. Bloor, *Org. Magn. Reson.* **2**, 491 (1970).

<sup>79</sup> M. Alexandre and P. Rigny, *Mol. Cryst. Liq. Cryst.* **17**, 19 (1972).

<sup>80</sup> E. O. Fischer, H. A. Goodwin, C. G. Kreiter, H. D. Simmons, K. Sonogashira, and S. B. Wild, *J. Organomet. Chem.* **14**, 359 (1968).

<sup>81</sup> M. Huke and K. Görlitzer, *Arch. Pharm. (Weinheim, Ger.)* **302**, 423 (1969).

acetone); in the 2-phenyl derivative, enolization is complete.<sup>82</sup> Compounds **1** (X = CHNHR, Y = O or S; X = O, Y = CHNHR<sup>83</sup>; X = O, Y = N<sup>15</sup>NHPh<sup>84</sup>) exist mainly as the oxo (or thioxo) form in organic solvents. The 2-arylmethylene derivatives **1** (5-Me; X = O, Y = CHAr), obtained from 5-methylthioindoxyl and an aromatic aldehyde, have the Z-configuration.<sup>85</sup>

b. <sup>13</sup>C NMR. The spectra of benzo[b]thiophene and various methyl derivatives have been assigned by three groups of workers with the aid of specifically deuterated compounds<sup>86-88</sup>; a fourth assignment appears to be erroneous.<sup>89</sup> Steric effects in peri-substituted compounds have been compared with analogous effects in naphthalene and benzo[b]furan.<sup>88</sup> There is evidence that benzo[b]thiophene has greater aromaticity than the oxygen analog.<sup>86</sup>

The spectra of substituted benzo[b]thiophene 1-oxides and 1,1-dioxides confirm the expected decrease in aromaticity as the oxidation state of the sulfur atom is successively increased.<sup>90</sup>

<sup>13</sup>C-NMR data have been obtained for thioindoxyl<sup>91</sup> and benzo[b]thiophene-2,3-dione<sup>58</sup>; detailed <sup>1</sup>H-NMR data are also available for the latter compound.<sup>57</sup>

## 2. Mass Spectra

There has been surprisingly little interest in this area. Spectra of the following have been recorded: aryloxy, arylthio, arylsulfonyl, and dialkylamino derivatives of 2,3-dimethylbenzo[b]thiophene<sup>92</sup>; 2-bromobenzo[b]thiophene-3-carboxaldehyde and 2-bromo-3-(dibromomethyl)benzo[b]thiophene<sup>93</sup>; several chloro- and phenylbenzo[b]thiophenes and their

<sup>82</sup> B. Stridsberg and S. Allenmark, *Chem. Scr.* **9**, 216 (1976).

<sup>83</sup> V. S. Bogdanov, V. P. Litvinov, Ya. L. Gol'dfarb, N. N. Petuchova, and E. G. Ostapenko, *J. Prakt. Chem.* **316**, 970 (1974).

<sup>84</sup> C. H. Yoder, R. C. Barth, W. M. Richter, and F. A. Snively, *J. Org. Chem.* **37**, 4121 (1972).

<sup>85</sup> L. S. S. Réamonn and W. I. O'Sullivan, *J. C. S. Perkin I*, 1009 (1977).

<sup>86</sup> N. Platzter, J.-J. Basselier, and P. Demerseman, *Bull. Soc. Chim. Fr.*, 905 (1974).

<sup>87</sup> A. V. Anisimov, Yu. N. Luzikov, V. M. Nikolaeva, Yu. N. Radyukin, E. A. Karakhanov, and E. A. Viktorova, *Khim. Geterotsikl. Soedin.*, 1625 (1977).

<sup>88</sup> P. D. Clark, D. F. Ewing, and R. M. Scrowston, *Org. Magn. Reson.* **8**, 252 (1976).

<sup>89</sup> L. Kiezel, M. Liszka, and M. Rutkowski, *Spectrosc. Lett.* **12**, 45 (1979).

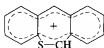
<sup>90</sup> P. Geneste, J.-L. Olivé, S. N. Ung, M. E. El Faghi, J. W. Easton, H. Beierbeck, and J. K. Saunders, *J. Org. Chem.* **44**, 2887 (1979).

<sup>91</sup> M. S. Chauhan and I. W. J. Still, *Can. J. Chem.* **53**, 2880 (1975).

<sup>92</sup> B. S. Thyagarajan and K. C. Majumdar, *Phosphorus Sulfur* **1**, 55 (1976).

<sup>93</sup> R. Neidlein, H. Heid, and A. Hotzel, *Arch. Pharm. (Weinheim, Ger.)* **310**, 689 (1977).

1,1-dioxides<sup>94</sup>; some substituted 6- and 7-nitrobenzo[*b*]thiophene 1,1-dioxides<sup>95</sup>; and 6-amino-2,3-dimethylbenzo[*b*]thiophene 1,1-dioxide.<sup>96</sup>



(2)

The molecular ion of 3-phenylbenzo[*b*]thiophene gives the rearranged  $14\pi$  ion **2** prior to fragmentation.<sup>97</sup> The mode of fragmentation of the 2,3-dideutero derivative suggested that all of the hydrogens in benzo[*b*]thiophene were randomized prior to the loss of ethyne from the molecular ion.<sup>98</sup> However, later studies on benzo[*b*]thiophene-2-[<sup>13</sup>C] have shown that this randomization is undoubtedly due to carbon scrambling.<sup>99</sup>

### 3. IR Spectra

Mille *et al.* determined the frequencies and symmetry types of the normal modes of vibration of benzo[*b*]thiophene and benzo[*b*]furan by analysis of their spectra in the range  $200\text{--}4000\text{ cm}^{-1}$  and proposed firm assignments in all but a few cases.<sup>100</sup> Symmetry assignments were based on the Raman spectra of the compounds in the liquid state (together with the depolarization ratios) and on IR spectra (especially in the vapor state).

For a range of 3-substituted benzo[*b*]thiophenes, a linear relationship has been found between the integrated intensity (*A*) of the IR band at  $1264\text{ cm}^{-1}$  and the appropriate  $\sigma^p$  substituent constant.<sup>101</sup> The result is somewhat surprising, since it is more usual to relate this substituent constant to  $\sqrt{A}$ .<sup>102</sup> The carbonyl stretching frequencies for the monomeric and dimeric forms

<sup>94</sup> V. S. Fal'ko, V. I. Khvostenko, V. Udre, and M. G. Voronkov, *Khim. Geterotsykl. Soedin.* **7**, 326 (1971).

<sup>95</sup> I. U. Numanov, A. Kh. Kadyrov, A. A. Bakaev, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **18**, 22 (1975).

<sup>96</sup> A. A. Bakaev, I. U. Numanov, A. Kh. Kadyrov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **18**, 25 (1975).

<sup>97</sup> E. S. Brodskii, R. A. Khmel'nitskii, A. A. Polyakova, and I. A. Mikhailov, *J. Org. Chem. USSR (Engl. Transl.)* **5**, 955 (1969).

<sup>98</sup> R. G. Cooks, I. Howe, S. W. Tam, and D. H. Williams, *J. Am. Chem. Soc.* **90**, 4064 (1968).

<sup>99</sup> R. G. Cooks and S. L. Bernasek, *J. Am. Chem. Soc.* **92**, 2129 (1970).

<sup>100</sup> G. Mille, G. Davidovics, and J. Chouteau, *J. Chim. Phys. Phys.-Chim. Biol.* **69**, 1662 (1972).

<sup>101</sup> N. Kucharczyk, B. Kakac, and V. Horak, *Collect. Czech. Chem. Commun.* **34**, 2959 (1969).

<sup>102</sup> T. L. Brown, *J. Phys. Chem.* **64**, 1798 (1960).

of benzo[b]furan-2-carboxylic acid have been determined; the values decrease steadily as the heteroatom is replaced successively by S, Se, and Te.<sup>103</sup> A detailed vibrational analysis of benzo[b]thiophene-2,3-dione has been made on the basis of IR and Raman spectral data.<sup>104</sup>

#### 4. UV Spectra

The hybrid character and rotational structure of the  $\pi^* \leftarrow \pi$  transitions of benzo[b]thiophene have been analyzed in detail.<sup>105</sup> For benzo[b]thiophene, the absorption spectra of the triplet state and of the anion have been recorded after flash photolysis and  $\gamma$ -irradiation (<sup>60</sup>Co), respectively.<sup>106,107</sup>

The tautomerism of thioindoxyl has been investigated by a UV method.<sup>108</sup> Freshly prepared thioindoxyl exists entirely in the oxo form and enolizes very slowly in aprotic solvents. The degree of enolization in solution depends, *inter alia*, on the age of the sample of thioindoxyl and on whether equilibrium has been reached before measurements are made; these factors are probably responsible for some of the conflicting results reported in the past (cf. Ref. 2).

The fact that 2-methylbenzo[b]thiophene is reversibly protonated in sulfuric acid has enabled its basicity ( $pK_a \approx -10.4$ ) to be estimated spectrophotometrically.<sup>109</sup>

The UV absorption of isomeric acetylbenzo[b]thiophenes has been discussed as a means of complementing the NMR method<sup>72</sup> for locating the position of an acetyl substituent.<sup>110</sup> The spectra of 2,3-dihydrobenzo[b]thiophene 1-oxide<sup>111</sup> and 1,1-dioxide<sup>112</sup> have been investigated.

For the charge-transfer spectra of the complexes of some 3-substituted benzo[b]thiophenes with tetracyanoethene, a linear correlation exists between  $\sigma_p^+$  substituent constants and the wave number of the first absorption maximum.<sup>101</sup>

<sup>103</sup> F. Fringuelli and A. Taticchi, *J. Heterocycl. Chem.* **10**, 89 (1973).

<sup>104</sup> A. Bigotto and V. Galasso, *Spectrochim. Acta, Part A* **34**, 923 (1978).

<sup>105</sup> A. Hartford, A. R. Muirhead, and J. R. Lombardi, *J. Mol. Spectrosc.* **35**, 199 (1970).

<sup>106</sup> F. C. Thyron, *J. Phys. Chem.* **77**, 1478 (1973).

<sup>107</sup> J. Wendenburg and H. Möckel, *Z. Naturforsch., Teil B* **23**, 1171 (1968).

<sup>108</sup> W. Rubaszewska and Z. R. Grabowski, *Tetrahedron* **25**, 2807 (1969).

<sup>109</sup> M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron* **32**, 1767 (1976).

<sup>110</sup> P. Faller, *Bull. Soc. Chim. Fr.*, 941 (1969).

<sup>111</sup> G. Kresze and W. Amann, *Spectrochim. Acta, Part A* **26**, 647 (1970).

<sup>112</sup> G. Kresze and W. Amann, *Spectrochim. Acta, Part A* **25**, 393 (1969).

### 5. Photoelectron Spectra

Theoretical aspects of UV-PE spectra have been discussed in Section II.A. Photoelectronic spectroscopy can give information on molecular conformation, as well as on electronic structures. Thus, it has been deduced that 2- and 3-acetylbenzo[b]thiophenes are planar, whereas the 2-phenyl derivative is not.<sup>33</sup>

### C. PHYSICAL MEASUREMENTS

The molecular dimensions of benzo[b]thiophene have not yet been reported. The structures of *N*-(3-phenyl-2-benzo[b]thienyl)benzenecarbothioamide<sup>113</sup> and 5-bromo-2,3-dimethylbenzo[b]thiophene have been established by X-ray crystallography; in the latter, the two rings are inclined at 0.6° to each other.<sup>114</sup> Crystallographic data are available for the 1:1 molecular complex formed between benzo[b]thiophene-3-carboxaldehyde and 1,3,5-trinitrobenzene<sup>115</sup> and for the 1,1-dioxides of the following: benzo[b]thiophene<sup>116,117</sup> (showing that the SO bonds are arranged approximately tetrahedrally around the sulfur atom<sup>116</sup>), 3,5-dimethyl- and 2,3,5-trimethylbenzo[b]thiophene,<sup>118</sup> 2,3-dihydrobenzo[b]thiophene,<sup>117</sup> and 2,2-dimethylthioindoxyl.<sup>119</sup>

Dipole moments of benzo[b]thiophene and of several of its alkyl, phenyl, and 1,1-dioxide derivatives have been determined.<sup>120,121</sup> The conformations of benzo[b]thiophene-3-thiol and its *S*-methyl derivative<sup>122</sup> and of benzo[b]thiophene-2-carboxaldehyde have been studied by dipole moments.<sup>123</sup>

<sup>113</sup> Gy. Argay and A. Kalman, *Cryst. Struct. Commun.* **2**, 19 (1973).

<sup>114</sup> J. H. C. Hogg and H. H. Sutherland, *Acta Crystallogr., Sect. B* **30**, 2058 (1974).

<sup>115</sup> R. Pascard and C. Pascard-Billy, *Acta Crystallogr., Sect. B* **28**, 1926 (1972).

<sup>116</sup> R. L. R. Towns and S. H. Simonsen, *Cryst. Struct. Commun.* **3**, 373 (1974).

<sup>117</sup> L. M. Kim, I. U. Numanov, and I. M. Nasyrov, *Izv. Akad. Nauk Tadzh. SSR, Otd. Fiz.-Mat. Geol.-Khim. Nauk*, **118** (1979) [*CA* **92**, 102572 (1980)].

<sup>118</sup> I. U. Numanov, Kh. M. Kurbanov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **13**, 38 (1970).

<sup>119</sup> L. Preuss, W. Hoppe, S. Hechtischer, and K. Zechmeister, *Acta Crystallogr., Sect. B* **27**, 920 (1971).

<sup>120</sup> L. M. Kim, I. U. Numanov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **20**, 28 (1977) [*CA* **88**, 135994 (1978)].

<sup>121</sup> M. G. Grunfest, Yu. V. Kolodyazhnyi, V. E. Udre, M. G. Voronkov, and O. A. Osipov, *Khim. Geterotsikl. Soedin.*, 448 (1970).

<sup>122</sup> H. Lumbroso, D. M. Bertin, and P. Cagniant, *Bull. Soc. Chim. Fr.*, 1720 (1970).

<sup>123</sup> C. G. Andrieu and A. Ruwet, *Bull. Soc. Chim. Fr.*, 1008 (1972).

Measurements of molecular magnetic anisotropies, determined in solution by depolarized Rayleigh scattering,<sup>124</sup> and of magneto-optical rotatory dispersion<sup>125</sup> and magnetic circular dichroism<sup>125a</sup> have confirmed that the  $\pi$ -electron delocalization in benzo[*b*]thiophene is greater than that in benzo[*b*]furan.

The enthalpies of combustion of benzo[*b*]thiophene<sup>126</sup> and of some benzo[*b*]thiophene 1,1-dioxides<sup>127,128</sup> have been determined and used to calculate the enthalpies of formation in the solid phase. For the parent compound, the enthalpy of sublimation has been determined calorimetrically, and the enthalpy of formation in the vapor phase and the bond energy of the C—S bond have been calculated.<sup>129</sup>

### III. Miscellaneous Reactions and Properties of Benzo[*b*]thiophenes

#### A. ADDITION REACTIONS

##### 1. Additions to the 2,3-Bond (Excluding Cycloadditions)

Benzo[*b*]thiophene undergoes ionic addition of hydrogen by treatment with  $\text{Et}_3\text{SiH}$  in  $\text{CF}_3\text{CO}_2\text{H}$ <sup>130</sup>; the 2- and 3-methyl derivatives react similarly, and with  $\text{Ph}_2\text{SiD}_2$  undergo addition of HD, the deuterium atom being incorporated specifically on the alkyl-substituted carbon atom.<sup>131</sup> The first wave in the polarographic reduction of benzo[*b*]thiophene corresponds to a 2-electron reduction to the 2,3-dihydro compound.<sup>132</sup> Electrochemical oxidation of benzo[*b*]thiophene in methanol gives mainly 2,3-dihydro-2,3-

<sup>124</sup> J.-P. Canselier and C. Clement, *J. Chim. Phys. Phys.-Chim. Biol.* **75**, 880 (1978).

<sup>125</sup> P. Cassoux, J.-P. Canselier, and M.-F. Bruniquel, *Bull. Soc. Chim. Fr.*, 2379 (1974).

<sup>125a</sup> M. A. Souto, S. L. Wallace, and J. Michl, *Tetrahedron* **36**, 1521 (1980).

<sup>126</sup> W. D. Good, *J. Chem. Eng. Data* **17**, 158 (1972).

<sup>127</sup> S. Nuritdinov, I. U. Numanov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **16**, 34 (1973).

<sup>128</sup> L. M. Kim, I. U. Numanov, and I. M. Nasyrov, *Izv. Akad. Nauk Tadzh. SSR, Otd. Fiz.-Mat. Geol.-Khim. Nauk*, 118 (1979) [*CA* **92**, 93769 (1980)].

<sup>129</sup> R. Sabbah, *Bull. Soc. Chim. Fr., Pt. 1*, 434 (1979).

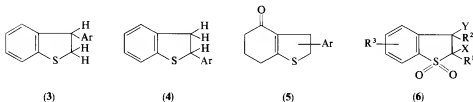
<sup>130</sup> D. N. Kursanov, Z. N. Parnes, G. I. Bolestova, and L. I. Belen'kii, *Tetrahedron* **31**, 311 (1975).

<sup>131</sup> G. I. Bolestova, A. N. Korepanov, Z. N. Parnes, and D. N. Kursanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2547 (1974).

<sup>132</sup> S. G. Mairanovskii, L. I. Kosychenko, and V. P. Litvinov, *Elektrokhimiya* **15**, 118 (1979) [*CA* **91**, 123131 (1979)].

dimethoxybenzo[*b*]thiophene (mixture of *cis* and *trans* isomers), the 3-methyl and 2,3-dimethyl derivatives behave similarly.<sup>133</sup> In the presence of sodium, a cyclic secondary amine will add to benzo[*b*]thiophenes, to give the 2-(*N*-substituted) derivative.<sup>134</sup> In contrast, benzo[*b*]thiophene is reported to undergo photoaddition of primary and secondary amines in the opposite direction, to give the 3-amine.<sup>135,136</sup> NMR spectroscopy has confirmed that the chlorination of 2,3-dimethylbenzo[*b*]thiophene<sup>2</sup> (to 2-chloromethyl-3-methylbenzo[*b*]thiophene) proceeds via an adduct of the halogen at the 2,3-bond.<sup>137</sup>

At 20°C in CS<sub>2</sub> or CH<sub>2</sub>Cl<sub>2</sub>, or at 0°C in benzene, benzo[*b*]thiophene undergoes self-addition in the presence of AlCl<sub>3</sub>, to give a mixture of two or more of the dimers **3** and **4** (Ar = 2- or 3-benzo[*b*]thienyl).<sup>138</sup> At 20°C in benzene, the dimers are accompanied by the benzene addition products **3** and **4** (Ar = Ph). With AlCl<sub>3</sub> in toluene, ethylbenzene, and 1,2- or 1,4-dimethylbenzene at 20°C, there is no dimerization, and only the addition products **3** and **4** (Ar = *p*-tolyl etc.) are found; isomer **3** predominates in each case. It is believed that benzo[*b*]thiophene is protonated by moist AlCl<sub>3</sub>, and that the resulting electrophile reacts either with benzo[*b*]thiophene or with an aromatic substrate, to give the observed products. At 80°C, with AlCl<sub>3</sub> in either benzene or toluene, the fully aromatic 2-arylbenzo[*b*]thiophene is formed in good yield.<sup>138</sup> Use of chlorobenzene in the above reactions gives only dimeric products. Other workers, however, claim that 6,7-dihydrobenzo[*b*]thiophene-4-(5*H*)-one undergoes AlCl<sub>3</sub>-catalyzed addition of either benzene or chlorobenzene, to give the dihydro products **5** (Ar = 2- or 3-Ph or C<sub>6</sub>H<sub>4</sub>·Cl-*p*).<sup>139</sup>



<sup>133</sup> J. Srogl, M. Janda, I. Stibor, J. Kos, and V. Vyskocil, *Collect. Czech. Chem. Commun.* **43**, 2015 (1978).

<sup>134</sup> P. Grandclaude and A. Lablache-Combiere, *J. Org. Chem.* **43**, 4379 (1978).

<sup>135</sup> P. Grandclaude, A. Lablache-Combiere, and C. Parkanyi, *Tetrahedron* **29**, 651 (1973).

<sup>136</sup> A. Lablache-Combiere, A. Pollet, and D. Lerner, *J. Chem. Res. (S)*, 38; (*M*), 281 (1978).

<sup>137</sup> E. Baciocchi, S. Clementi, and G. V. Sebastiani, *J. C. S. Perkin II*, 266 (1976).

<sup>138</sup> P. D. Clark, K. Clarke, D. F. Ewing, and R. M. Scowston, *J. C. S. Perkin I*, 677 (1980).

<sup>139</sup> Ya. L. Gol'dfarb, B. P. Fabrichnyi, V. K. Zav'yalova, and V. S. Bogdanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1570 (1979).



Although benzo[*b*]thiophene 1,1-dioxide fails to undergo  $\text{AlCl}_3$ -catalyzed addition of  $\text{ArH}$ ,<sup>138</sup> it is said to give the 3-substituted addition product **3** (1,1-dioxide) in the presence of sulfuric acid.<sup>140</sup> Substituted benzo[*b*]thiophene 1,1-dioxides react with  $\text{HBr}$  (in the presence of  $\text{H}_2\text{O}_2$ ),<sup>141</sup>  $\text{ArSCl}$ , or  $\text{ArSH}$ <sup>142</sup> to give the appropriate addition product **6** ( $\text{X} = \text{Br}$  or  $\text{SAr}$ ,  $\text{Y} = \text{H}$  or  $\text{Cl}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ). At an appropriate pH, benzo[*b*]thiophene 1,1-dioxide is reduced at a mercury cathode in DMF to give the 2,3-dihydro derivative (98%).<sup>143</sup> 3-Substituted benzo[*b*]thiophene 1,1-dioxides undergo overall hydration when treated with hydroperoxide ion (from  $\text{H}_2\text{O}_2$ -aq.  $\text{NaOH}$ -pyridine), but the products **6** ( $\text{R}^1 = \text{R}^3 = \text{X} = \text{H}$ ,  $\text{Y} = \text{OH}$ ) probably arise via hydroperoxide intermediates.<sup>144</sup>

## 2. Benzo[*b*]thiophenium Salts

Benzo[*b*]thiophenium salts **7** are included in this section because they are formally obtained by the addition of  $\text{R}^1\text{X}$  to the sulfur atom. In practice, alkylation is difficult and is achieved by the use of an alkyl iodide in the presence of  $\text{AgClO}_4$ ,  $\text{AgBF}_4$ ,<sup>145</sup> or  $\text{AgPF}_6$ .<sup>146</sup> *S*-Methyl salts are obtained directly by using trimethyloxonium<sup>145</sup> or *O*-methylidibenzofuranium tetrafluoroborate.<sup>147</sup> NMR spectroscopy shows that the methylene protons of the ethyl group in a 2-substituted *S*-ethylbenzo[*b*]thiophenium salt **7** ( $\text{R}^1 = \text{Et}$ ,  $\text{R}^2 \neq \text{H}$ ) are magnetically nonequivalent, indicating that the sulfur atom is  $sp^3$ -hybridized.<sup>145</sup> One orbital would then contain a lone pair of electrons, which cannot interact significantly with the  $\pi$ -electrons of the ring, for then the *S*-substituent would tend to become coplanar with the ring. In the NMR spectrum, H-3 resonates at a much lower field strength than H-2, suggesting that structure **7a** is only a minor contributor to the overall hybrid. The salts readily decompose to the parent heterocycle in hydroxylic solvents; *S*-methyl salts are powerful methylating agents. The 2,3-bond evidently possesses some olefinic character, since the *S*-methyl salt **7** ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$ ) undergoes addition of bromine, as well as substitution.<sup>145</sup>

<sup>140</sup> R. Usmanov, I. U. Numanov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **19**, 35 (1976).

<sup>141</sup> K. V. Legeido, I. U. Numanov, I. M. Nasyrov, and S. S. Dzhulolov, *Dokl. Akad. Nauk Tadzh. SSR* **20**, 36 (1977).

<sup>142</sup> I. U. Numanov, U. K. Karimov, and I. M. Nasyrov, *Izv. Akad. Nauk Tadzh. SSR, Otd. Fiz.-Mat. Geol.-Khim. Nauk*, 52 (1973) [*CA* **80**, 82550 (1974)].

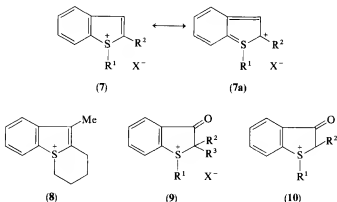
<sup>143</sup> K. Ankner, B. Lamm, and J. Simonet, *Acta Chem. Scand., Ser. B* **31**, 742 (1977).

<sup>144</sup> S. Marmor, *J. Org. Chem.* **42**, 2927 (1977).

<sup>145</sup> R. M. Acheson and D. R. Harrison, *J. Chem. Soc. C*, 1764 (1970).

<sup>146</sup> J. A. Cotruvo and I. Degani, *J. C. S. Chem. Commun.*, 436 (1971).

<sup>147</sup> A. J. Copson, H. Heaney, A. A. Logun, and R. P. Sharma, *J. C. S. Chem. Commun.*, 315 (1972).



2-(4-Iodobutyl)-3-methylbenzo[*b*]thiophene will undergo intramolecular cyclization with  $\text{AgPF}_6$  or  $\text{AgClO}_4$ , to give the salt **8**,<sup>146</sup> but it has not been possible to carry out such a cyclization with an  $\omega$ -halogeno 7-side chain.<sup>148</sup> 2,3-Dibromobenzo[*b*]thiophene 1-oxide is *O*-methylated by  $\text{MeI}-\text{AgClO}_4-\text{MeCN}$ , to give the corresponding *S*-methoxy salt.<sup>149</sup>

The salts **9** ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ) can be prepared directly from thioindoxyl,<sup>150</sup> or less conventionally by simultaneous *S*-methylation and *O*-demethylation of 3-methoxybenzo[*b*]thiophene with  $\text{MeI}-\text{AgClO}_4$ .<sup>148</sup> The thioindoxyl salt **9** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ) is obtained by treating  $\omega$ -diazo-(2-phenylthio)acetophenone with  $\text{HClO}_4$ ; it is readily deprotonated by  $\text{Et}_3\text{N}$ , to give the ylide **10** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ).<sup>151</sup> 2-Nitro- and 2,4-dinitrobenzenesulfonyl chloride ( $\text{ArSOCl}$ ) react either with  $\omega$ -diazo-(2-phenylthio)acetophenone or with the 2-unsubstituted compound **10** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ), to give the substituted ylides **10** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{SAr}$ ).<sup>152</sup> 2,2-Dimethylthioindoxyl reacts with *O*-mesitylenesulfonylhydroxylamine ( $\text{NH}_2\text{OMes}$ ) to give the salt **9** ( $\text{R}^1 = \text{NH}_2$ ,  $\text{R}^2 = \text{R}^3 = \text{Me}$ ,  $\text{X} = \text{OMes}$ ), which is rearranged by  $\text{K}_2\text{CO}_3-\text{DMF}$  to 2-(1,2-benzisothiazol-3-yl)propene (75%).<sup>153</sup>

Benzo[*b*]thiophene reacts with dimethyl diazomalonate in the presence of rhodium(II) acetate, to give the ylide **7** [ $\text{R}^1 = \text{C}(\text{CO}_2\text{Me})_2$ ,  $\text{R}^2 = \text{H}$ ] (97%).<sup>154</sup>

<sup>148</sup> R. M. Acheson and M. W. Cooper, *J. C. S. Perkin I*, 1185 (1980).

<sup>149</sup> R. M. Acheson and J. K. Stubbs, *J. C. S. Perkin I*, 899 (1972).

<sup>150</sup> B. Stridsberg and S. Allenmark, *Chem. Scr.* **6**, 184 (1974).

<sup>151</sup> W. T. Flowers, G. Holt, and M. A. Hope, *J. C. S. Perkin I*, 1116 (1974).

<sup>152</sup> W. T. Flowers, G. Holt, and P. P. McCleery, *J. C. S. Perkin I*, 446 (1978).

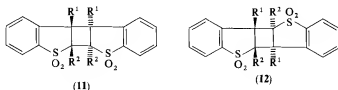
<sup>153</sup> Y. Tamura, S. M. Bayomi, C. Mukai, M. Ikeda, M. Murase, and M. Kise, *Tetrahedron Lett.* **21**, 533 (1980).

<sup>154</sup> R. J. Gillespie and A. E. A. Porter, *J. C. S. Perkin I*, 2624 (1979).

### 3. Cycloaddition Reactions

*Note:* Reactions discussed in the following sections do not necessarily proceed by a concerted mechanism.

a.  $[\pi 2 + \pi 2]$ -Cycloadditions. The photodimerization of benzo[*b*]thiophene 1,1-dioxide has been known for some time.<sup>2</sup> It has now been shown that the major product **11** ( $R^1 = R^2 = H$ ), resulting from head-to-head (HH) linking of the monomer, is accompanied by the head-to-tail (HT) linked isomer **12** ( $R^1 = R^2 = H$ ) (ratio 73:27).<sup>155</sup> The reaction proceeds via attack by the triplet excited state on the ground-state molecule<sup>156</sup>; it shows an external heavy-atom effect.<sup>157</sup> In contrast, the photodimerization of 2-bromobenzo[*b*]thiophene 1,1-dioxide in benzene gives only the HT product **12** ( $R^1 = H, R^2 = Br$ ); in its formation an exciplex mechanism competes with that just described for the case of the parent compound.<sup>157</sup> Irradiation of 2-methylbenzo[*b*]thiophene 1,1-dioxide gives the HH and HT products **11** and **12** ( $R^1 = H, R^2 = Me$ ) [ratio 9:1 (or 1:1 if  $O_2$  is present)].<sup>158</sup> Benzo[*b*]thiophene-3-carboxylic acid 1,1-dioxide is dimerized by light and by heat, to give the HH product **11** ( $R^1 = CO_2H, R^2 = H$ ).<sup>159</sup> 3-Methylbenzo[*b*]thiophene 1-oxide undergoes photodimerization to give two HH products **11** ( $R^1 = Me, R^2 = H$ ; SO instead of  $SO_2$ ), in which the two  $S=O$  bonds are either cis or trans with respect to each other.<sup>160</sup> The same sulfone **11** ( $R^1 = Me, R^2 = H$ ) is obtained by oxidation of either isomer and by photodimerization of 3-methylbenzo[*b*]thiophene 1,1-dioxide.



Unsymmetrically substituted alkenes add regio- and stereospecifically to benzo[*b*]thiophene 1,1-dioxide.<sup>161</sup> The product **13** from trichloroethene undergoes elimination of HCl with  $Et_3N$ , to give the cyclobutene derivative

<sup>155</sup> D. N. Harpp and C. Heitner, *J. Org. Chem.* **35**, 3256 (1970).

<sup>156</sup> D. N. Harpp and C. Heitner, *J. Am. Chem. Soc.* **94**, 8179 (1972).

<sup>157</sup> W. W. Schloman and B. F. Plummer, *J. Am. Chem. Soc.* **98**, 3254 (1976).

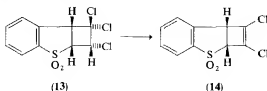
<sup>158</sup> M. J. Hopkinson, W. W. Schloman, B. F. Plummer, E. Wenkert, and M. Raju, *J. Am. Chem. Soc.* **101**, 2157 (1979).

<sup>159</sup> W. Davies, B. C. Ennis, C. Mahavera, and Q. N. Porter, *Aust. J. Chem.* **30**, 173 (1977).

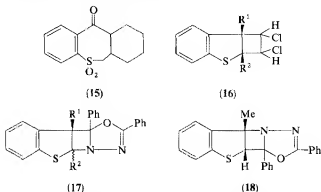
<sup>160</sup> M. S. El Faghi El Amoudi, P. Geneste, and J. L. Olivé, *Tetrahedron Lett.*, 999 (1978).

<sup>161</sup> D. N. Harpp and C. Heitner, *J. Org. Chem.* **38**, 4184 (1973).

**14.** The photoaddition product of 3-acetoxybenzo[*b*]thiophene 1,1-dioxide with cyclohexene undergoes ring expansion in the presence of base, to give the benzothiepine derivative **15**.<sup>162</sup>



Like the 1,1-dioxides, the parent benzo[*b*]thiophenes will also undergo photoaddition of alkenes to give cyclobutane derivatives. In the sensitized addition of 1,2-dichloroethene, the four possible stereoisomers **16** are formed; which one predominates depends on the stereochemistry of the starting alkene.<sup>163</sup> Those isomers which can undergo trans elimination of HCl will react with base to give the cyclobutene derivative (cf. **14**). Benzo[*b*]thiophene will add photochemically across the C=N bond of 2,5-diphenyl-1,3,4-oxadiazole in the presence of a sensitizer, to give the trans-fused adduct **17** [ $R^1 = R^2 = H$  (trans)].<sup>164</sup> Sensitized addition to 2- or 3-methylbenzo[*b*]thiophene gives the more usual cis-fused products **17** [ $R^1 = H, R^2 = Me$  (cis)] and **17** [ $R^1 = Me, R^2 = H$  (cis)] respectively. However, with 3-methylbenzo[*b*]thiophene in the presence of iodine, the orientation of addition is reversed and the cis adduct **18** is obtained. 3-Pyrrolidinobenzo[*b*]thiophene



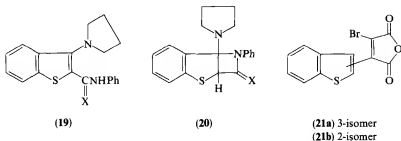
shows enamine-like character and undergoes thermal cycloaddition of PhNCO or PhNCS to give the amines **19** ( $X = O$  or  $S$ ), which are probably

<sup>162</sup> N. V. Kirby and S. T. Reid, *J. C. S. Chem. Commun.*, 150 (1980).

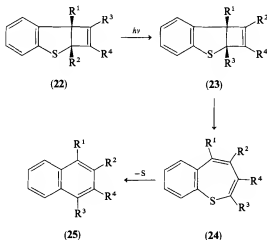
<sup>163</sup> D. C. Neckers, J. H. Dopfer, and H. Wynberg, *J. Org. Chem.*, **35**, 1582 (1970).

<sup>164</sup> K. Oe, M. Tashiro, and O. Tsuge, *Bull. Chem. Soc. Jpn.*, **50**, 3281 (1977).

formed from the adducts **20** ( $X = O$  or  $S$ ) by a hydrogen transfer reaction.<sup>165</sup> Benzo[*b*]thiophene reacts photochemically with dibromomaleic anhydride, to give the substitution product **21a** in addition to the expected all-*cis* cycloadduct.<sup>166</sup> Heating the cycloadduct gives **21b**.



The photoaddition reactions (Scheme 1) of benzo[*b*]thiophenes with alkynes ( $R^3C\equiv CR^4$ ) have been extensively studied. In some cases, the unrearranged adducts **22** ( $R^1 = R^2 = H$ ,  $R^3 = R^4 = Ph$ <sup>167</sup>;  $R^1 = H$ ,  $R^2 = Me$ ,  $R^3$  and  $R^4 = Ph$  or  $CO_2Me$ <sup>168</sup>) are obtained in very low yield. Generally, only the rearranged cyclobutenes **23** are isolated; these may then decompose thermally via **24** to the naphthalenes **25**. With unsymmetrical alkynes,



SCHEME 1

<sup>165</sup> D. N. Reinhoudt and C. G. Kouwenhoven, *Recl. Trav. Chim. Pays-Bas* **93**, 321 (1974).

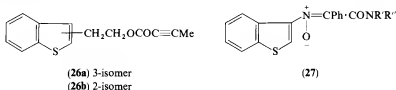
<sup>166</sup> T. Matsuo and S. Mihara, *Bull. Chem. Soc. Jpn.* **50**, 1797 (1977).

<sup>167</sup> W. H. F. Sasse, P. J. Collin, and D. B. Roberts, *Tetrahedron Lett.*, 4791 (1969).

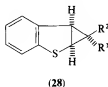
<sup>168</sup> A. H. A. Tinnemans and D. C. Neckers, *J. Org. Chem.* **43**, 2493 (1978).

cycloaddition may<sup>169</sup> or may not be regiospecific.<sup>168</sup> The alkyne **26a** undergoes intramolecular cycloaddition to give the expected unrearranged (2%) and rearranged adducts (42%); the 2-isomer **26b**, however, gives only the naphthalene derivative **25** ( $R^1 = \text{Me}$ ,  $R^2R^4 = \text{CO} \cdot \text{OCH}_2\text{CH}_2$ ,  $R^3 = \text{H}$ ).<sup>168</sup>

3-Pyrrolidinobenzo[*b*]thiophene reacts nonphotochemically with  $\text{MeO}_2\text{CC}\equiv\text{CCO}_2\text{Me}$  at  $-20^\circ\text{C}$  to give the unrearranged adduct **22**, which undergoes ring expansion to the benzo[*b*]thiepine **24** ( $R^1 = \text{pyrrolidino}$ ,  $R^2 = R^4 = \text{CO}_2\text{Me}$ ,  $R^3 = \text{H}$ ) in boiling ether; further heating in benzene gives the expected naphthalene derivative **25**.<sup>170</sup> The starting benzo[*b*]thiophenes discussed so far all contain ring-activating 2- or 3-substituents. It is also found that 3-nitrobenzo[*b*]thiophene will undergo a regiospecific thermal cycloaddition reaction with the ynamine,  $\text{PhC}\equiv\text{CN}R'R''$ , to give the unrearranged adduct **22** ( $R^1 = \text{NO}_2$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{NR}'R''$ ,  $R^4 = \text{Ph}$ ), which does not undergo ring expansion.<sup>171</sup> The nitron **27** is also formed (25%), probably by cycloaddition of the alkyne to the  $\text{N}=\text{O}$  bond of the 3- $\text{NO}_2$  group.



b. *Cheletropic Reactions.* The reaction of benzo[*b*]thiophene with the carbene,  $:\text{C}(\text{CO}_2\text{Et})_2$ , has been examined again (cf. Ref. 2).<sup>172</sup> Thermolysis of ethyl diazoacetate in liquid benzo[*b*]thiophene, with or without a copper catalyst, gives a mixture of esters (8%), from which the two stereoisomeric cyclopropane derivatives **28** ( $R^1$  or  $R^2 = \text{H}$  or  $\text{CO}_2\text{Et}$ ) and ethyl (3-benzo[*b*]thienyl)acetate have been isolated. In contrast to previous work,<sup>2</sup> no addition across the 4,5-bond was detected.

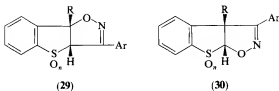


<sup>169</sup> J. H. Dopfer and D. C. Neckers, *J. Org. Chem.* **36**, 3755 (1971).

<sup>170</sup> D. N. Reinhoudt and C. G. Kouwenhoven, *Tetrahedron* **30**, 2431 (1974).

<sup>171</sup> D. N. Reinhoudt and C. G. Kouwenhoven, *Recl. Trav. Chim. Pays-Bas* **95**, 67 (1976).

<sup>172</sup> E. Wenkert, M. E. Alonso, H. E. Gottlieb, E. L. Sanchez, R. Pellicciari, and P. Cogolli, *J. Org. Chem.* **42**, 3945 (1977).



c. *1,3-Dipolar Cycloadditions.* Benzo[*b*]thiophene undergoes cycloaddition with a range of substituted benzonitrile oxides ( $\text{ArCN} \rightarrow \text{O}$ ), to give both orientational isomers **29** and **30** ( $\text{R} = \text{H}$ ,  $n = 0$ ).<sup>173</sup> If  $\text{Ar} = \text{Ph}$ , isomer **29** predominates (78:22)<sup>173</sup>; if  $\text{Ar} = \text{mesityl}$ <sup>173</sup> or 3,5-dichloro-2,4,6-trimethylphenyl,<sup>174</sup> isomer **30** predominates (74:26 and 70:30, respectively). The regiochemistry has been explained by a simple qualitative frontier orbital approach, which uses the highest occupied (HO) and lowest unoccupied (LU) orbital energies derived from experimental data.<sup>173,175</sup> Substituted benzo[*b*]thiophene 1-oxides<sup>176</sup> and 1,1-dioxides<sup>177</sup> undergo regiospecific cycloaddition with  $\text{ArCN} \rightarrow \text{O}$ , to give adducts **29** ( $\text{R} = \text{Me}$ ,  $n = 1$  or 2,  $\text{Ar} = \text{Ph}$  or mesityl). For 3-methylbenzo[*b*]thiophene 1-oxide, two isomers (1:1) of **29** ( $\text{R} = \text{Me}$ ,  $n = 1$ ,  $\text{Ar} = \text{mesityl}$ ) are obtained, corresponding to the two possible orientations of the  $\text{S}=\text{O}$  bond.<sup>176</sup>

Tetracyanoethene oxide, which behaves like a carbonyl ylide in cycloaddition reactions, gives the cycloadduct **31** with benzo[*b*]thiophene.<sup>178</sup>

Other reported 1,3-dipolar cycloadditions relate to benzo[*b*]thiophene 1,1-dioxide and occur regiospecifically. The following reagents have been used and the structure of each new ring is given in parentheses: the nitron,  $\text{ArCH}=\text{NO} \cdot \text{Ph}$  ( $\ddot{\text{O}}-\text{NPh}-\text{CHAr}$ ),<sup>177</sup> the diazo compound,  $\text{RCHN}_2$ <sup>179</sup> ( $\text{CHR}-\text{N}=\text{N}$  at room temperature;  $\text{CR}=\text{N}-\text{NH}$  at a higher temperature), and the nitrilimine,  $\text{ArN}^-\cdot\text{N}=\text{CR}^+$  ( $\text{NAr}-\text{N}=\text{CR}$ ).<sup>180</sup> The asterisk indicates the point of attachment of the new ring to C-3 of the parent benzo[*b*]thiophene ring. It can be seen that diazo compounds behave differently from the others, in that the negative end of the dipole becomes attached to the 2-position. The reaction of 2-benzoyl-3-chlorobenzo[*b*]thiophene 1,1-dioxide with diazomethane is of interest in that the first step is believed to

<sup>173</sup> P. Caramella, G. Cellerino, P. Grünanger, F. Marinone Albini, and M. R. ReCellerino, *Tetrahedron* **34**, 3545 (1978).

<sup>174</sup> P. L. Beltrame, M. G. Cattania, V. Redaelli, and G. Zecchi, *J. C. S. Perkin II*, 706 (1977).

<sup>175</sup> P. L. Beltrame, M. G. Cattania, and G. Zecchi, *Croat. Chem. Acta* **51**, 285 (1978).

<sup>176</sup> P. Geneste, R. Durand, and D. Pioch, *Tetrahedron Lett.*, 4845 (1979).

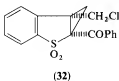
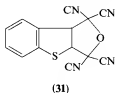
<sup>177</sup> F. Sauter and G. Büyüç, *Monatsh. Chem.* **105**, 254 (1974).

<sup>178</sup> S. Gronowitz and B. Uppström, *Acta Chem. Scand., Ser. B* **29**, 441 (1975).

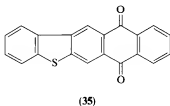
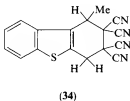
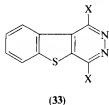
<sup>179</sup> F. Sauter and G. Büyüç, *Monatsh. Chem.* **105**, 550 (1974).

<sup>180</sup> F. Sauter, G. Büyüç, and U. Jordis, *Monatsh. Chem.* **105**, 869 (1974).

involve methylene insertion, to give the corresponding 3-chloromethyl compound, which then undergoes cycloaddition of diazomethane. The cycloadduct then loses nitrogen, to give the cyclopropane derivative **32**.<sup>181</sup>



d.  $[\pi 4 + \pi 2]$ -Cycloadditions. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate reacts with benzo[b]thiophene, then the cycloadduct readily loses nitrogen, and gives the tricycle **33** ( $X = \text{CO}_2\text{Me}$ ) (47%).<sup>182</sup> 3-Vinylbenzo[b]thiophene behaves as a conjugated diene, and undergoes normal Diels-Alder addition with ethenetetracarbonitrile.<sup>183</sup> 3-Methyl-2-vinylbenzo[b]thiophene behaves similarly, but the dienophile also undergoes  $[2 + 2]$ -cycloaddition with the vinyl double bond. 2-Methyl-3-vinylbenzo[b]thiophene, however, gives the rearranged adduct **34**, resulting from cycloaddition with a tautomeric form of the conjugated diene.<sup>183</sup> The normal adduct from 3-vinylbenzo[b]thiophene and 1,4-naphthoquinone undergoes base-catalyzed oxidative rearrangement to the linear quinone **35**.<sup>184</sup> 3-Vinylindene reacts with the 2,3-bond of benzo[b]thiophene 1,1-dioxide, to give the two possible endo orientational isomers.<sup>185</sup>



<sup>181</sup> W. Ried, J. B. Mavunkal, and G. Oremek, *Justus Liebigs Ann. Chem.*, 1274 (1978).

<sup>182</sup> G. Seitz and T. Kämpchen, *Arch. Pharm. (Weinheim, Ger.)* **309**, 679 (1976).

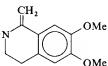
<sup>183</sup> W. H. Cherry, J. T. Craig, and Q. N. Porter, *Aust. J. Chem.* **32**, 133 (1979).

<sup>184</sup> W. H. Cherry and Q. N. Porter, *Aust. J. Chem.* **32**, 145 (1979).

<sup>185</sup> R. Bergamasco and Q. N. Porter, *Aust. J. Chem.* **30**, 1523 (1977).



TABLE I  
 PHOTOCYCLIZATION OF BENZO[*b*]THIOPHENE DERIVATIVES (cf. 36)

Z	2- or 3- X—Y	Ring D	Ref.	Notes
H	3-CH=CH	1- or 2-Naphthyl	186	<sup>a</sup>
H	3-CR=CR'	4-Pyridyl	187	
H	2-CH=CH	2-Benzo[ <i>b</i> ]thienyl	188	
		2-Naphtho[2,1- <i>b</i> ]thienyl	188	<sup>b</sup>
		2-Naphtho[2,1- <i>b</i> ]furyl	188	
H	2-CO—NH	2-, 3-, and 4-Pyridyl, 1-Naphthyl	189	<sup>c,d</sup>
Cl	2-CO—NH			
Cl	2-CO—NH	Substituted phenyl	189, 190	
H	2-CO—NH	Phenyl	189, 191	<sup>e</sup>
H			192	<sup>f</sup>

<sup>a</sup> When ring D = 1-naphthyl, cyclization takes place on to the 2-position of the naphthalene ring; with the 2-naphthyl isomer, cyclization takes place unexpectedly in the 3-position to give a linear pentacycle.

<sup>b</sup> The resulting heterohelicene is capable of optical resolution.

<sup>c</sup> With the 2-pyridyl substituent, cyclization takes place on to the N atom as well as into the 3-position.

<sup>d</sup> Yields are much improved when Z = Cl.

<sup>e</sup> Cyclization in the absence of O<sub>2</sub> gives a cis-dihydro ring B/C junction.<sup>191</sup>

<sup>f</sup> In the absence of O<sub>2</sub>, the bond derived from the terminal methylene group is saturated.

## B. PHOTOCYCLIZATION REACTIONS

The photocyclization of benzo[*b*]thiophene derivatives **36**, in which the X—Y side chain may also be in the 3-position, provides a useful route to the polycyclic compounds **37** (Eq. 1). Examples are given in Table I.<sup>186–192</sup>

<sup>186</sup> A. Croisy, P. Jacquignon, and F. Perin, *J. C. S. Chem. Commun.*, 106 (1975).

<sup>187</sup> A. Shafiee and A. Rashidbaigi, *J. Heterocycl. Chem.* **13**, 141 (1976).

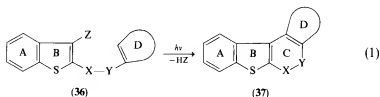
<sup>188</sup> M. B. Groen, H. Schadenberg, and H. Wynberg, *J. Org. Chem.* **36**, 2797 (1971).

<sup>189</sup> M. Terashima, K. Seki, K. Itoh, and Y. Kanaoka, *Heterocycles* **8**, 421 (1977).

<sup>190</sup> S. Kano, T. Ozaki, and S. Hibino, *Heterocycles* **12**, 489 (1979).

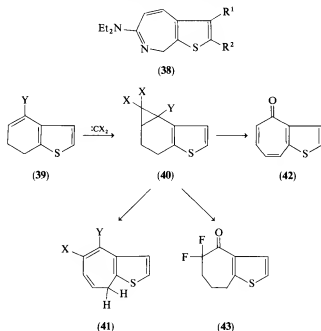
<sup>191</sup> Y. Kanaoka, K. Itoh, Y. Hatanaka, J. L. Flippen, I. L. Karle, and B. Witkop, *J. Org. Chem.* **40**, 3001 (1975).

<sup>192</sup> G. R. Lenz, *J. Heterocycl. Chem.* **16**, 433 (1979).



## C. RING-EXPANSION REACTIONS

Ring expansion via cycloaddition reactions has already been discussed (Section III,A,3,a). Irradiation of 6-azido-2,3-dibromobenzo[*b*]thiophene for 18 hours in Et<sub>2</sub>NH gives the 7-amino-6-diethylaminobenzo[*b*]thiophene derivative (13%); the same reaction in the presence of pyrene (triplet quencher) gives the ring-expanded product **38** (R<sup>1</sup> = R<sup>2</sup> = Br) (22%), which may be formed via an azirine intermediate.<sup>193</sup> Methyl 6-azidobenzo[*b*]thiophene-2-carboxylate gives a similar product **38** (R<sup>1</sup> = H, R<sup>2</sup> = CO<sub>2</sub>Me), but 6-azidobenzo[*b*]thiophene itself gives no ring-expanded products.



SCHEME 2

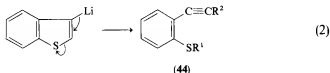
<sup>193</sup> B. Iddon, M. W. Pickering, H. Suschitzky, and D. S. Taylor, *J. C. S. Perkin I*, 1686 (1975).

The 6,7-dihydrobenzo[*b*]thiophenes **39** (Y = Me, Ph, OR, or OAc) react with dihalocarbenes, to give the cyclopropano compounds **40** (Scheme 2).<sup>194,195</sup> Heating **40** (X = Cl or Br, Y = Me, Ph, or OR) gives the corresponding 8*H*-cyclohepta[*b*]thiophene **41**.<sup>194</sup> Treatment of **40** (X = F, Y = OAc) with methanolic NaOH gives a mixture of the ketones **42** and **43**.<sup>195</sup>

Photolysis of 2,3-dihydro-2-methylbenzo[*b*]thiophene gives thiochroman as the major product.<sup>196</sup>

#### D. RING-FISSION REACTIONS

If an ethereal solution of 3-benzo[*b*]thienyllithium is kept at room temperature for 1 hour, it decomposes to give, *inter alia*, the thiolate anion **44** (R<sup>1</sup> = Li, R<sup>2</sup> = H) (Eq. 2); this can be methylated with Me<sub>2</sub>SO<sub>4</sub> to give the alkynes **44** (R<sup>1</sup> = Me, R<sup>2</sup> = H or Me).<sup>197</sup> If the solution is kept for



18 hours, then methylated, the products also include the *S*-butyl derivative **44** (R<sup>1</sup> = *n*-Bu, R<sup>2</sup> = Me), formed by alkylation of anion **44** (R<sup>1</sup> = Li, R<sup>2</sup> = H) with the *n*-BuBr generated when 3-benzo[*b*]thienyllithium is formed from 3-bromobenzo[*b*]thiophene and *n*-BuLi. 2-Methyl- and 2-phenyl-3-benzo[*b*]thienyllithium, and some of their 5-substituted derivatives, undergo similar ring-opening reactions.<sup>198,199</sup> Benzo[*b*]thiophene undergoes electrocyclic ring opening with lithium dimethylamide, to give the enamine **45** (X = Li, R = NMe<sub>2</sub>)<sup>200</sup>; similarly, 2,3-dihydrobenzo[*b*]thiophene and its 2-methyl derivative give **45** (X = Li, R = H or Me) with KNH<sub>2</sub> or LiNH<sub>2</sub>.<sup>201,202</sup> However, in a parallel reaction, benzo[*b*]thiophene under-

<sup>194</sup> C. F. Greco and V. G. Grosso, *J. Org. Chem.*, **38**, 146 (1973).

<sup>195</sup> P. Crabbé, A. Cervantes, A. Cruz, E. Galeazzi, J. Iriarte, and E. Velarde, *J. Am. Chem. Soc.*, **95**, 6655 (1973).

<sup>196</sup> D. C. Neckers and J. DeZwaan, *J. C. S. Chem. Commun.*, 813 (1969).

<sup>197</sup> R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 3447 (1971).

<sup>198</sup> R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 2592 (1970).

<sup>199</sup> R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 182 (1971).

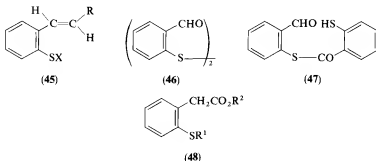
<sup>200</sup> A. E. M. Beyer and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas*, **96**, 178 (1977).

<sup>201</sup> H. Kloosterziel and J. A. A. van Drunen, *Tetrahedron Lett.*, 1023 (1973).

<sup>202</sup> E. A. Karakhanov, S. Kh. Sharipova, E. A. Viktorova, and M. V. Vagabov, *Vestn. Mosk. Univ., Khim.*, **19**, 98 (1978) [*CA* **89**, 108433 (1978)].

goes addition.<sup>134</sup> Benzo[*b*]thiophene undergoes a facile ring-opening reaction with anisole in the presence of  $\text{AlCl}_3$  at  $20^\circ\text{C}$ , to give **45** ( $\text{X} = \text{Me}$ ,  $\text{R} = \text{C}_6\text{H}_4\text{OMe-}p$ ) (89%).<sup>203</sup>

Ozonolysis of benzo[*b*]thiophene yields mainly the aldehydes **46** (34%) and **47** (22%).<sup>204</sup> Aldehyde **46**, which may also be obtained from benzenoid precursors, reacts with "active methylene" compounds of the type  $\text{RCH}_2\text{CO}_2\text{H}$  (e.g.,  $\text{R} = \text{CO}_2\text{H}$ ,  $\text{CN}$ ,  $\text{Ph}$ ) or  $\text{RCH}_3$  (e.g.,  $\text{R} = \text{NO}_2$ ), to give a 2-(*R*-substituted) benzo[*b*]thiophene. The reaction is of synthetic value in cases where the substituent *R* cannot easily be introduced by more conventional routes (e.g.,  $\text{R} = \text{NO}_2$ ).



Consistent with their thiolactone structure, benzo[*b*]thiophen-2-(3*H*)-one (thioxindole) derivatives readily undergo ring opening with  $\text{NaOH}$ , to give the anion **48** ( $\text{R}^1 = \text{R}^2 = \text{Na}$ ), which is alkylated on sulfur by  $\text{RX}^{205}$  and methylated on sulfur and on oxygen by  $\text{Me}_2\text{SO}_4$ .<sup>206</sup> Thioxindole reacts with chlorine to give the acyl chloride of the acid **48** ( $\text{R}^1 = \text{Cl}$ ,  $\text{R}^2 = \text{OH}$ )<sup>207</sup> and is reduced by  $\text{LiAlH}_4$  to 2-(2-mercaptophenyl)ethanol.<sup>208</sup> A 3-arylidene thioxindole **49** gives the intermediate **50** on treatment with base. The latter undergoes internal Michael addition, to give a 2-aryl-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic acid.<sup>209</sup> If the aryl residue in **50** has an *o*-hydroxyl group, an unsaturated lactone is formed, Michael addition on to which gives the product **51**.<sup>210</sup>

2,3-Dihydrobenzo[*b*]thiophene 1,1-dioxide undergoes electrochemical cleavage of the aryl-sulfur bond,<sup>211</sup> to give the sulfinate anion,

<sup>203</sup> P. D. Clark, Ph.D. Thesis, Hull (1976).

<sup>204</sup> K. J. Brown and O. Meth-Cohn, *Tetrahedron Lett.*, 4069 (1974).

<sup>205</sup> W. C. Lumma and G. A. Berchtold, *J. Org. Chem.*, **34**, 1566 (1969).

<sup>206</sup> R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 1926 (1970).

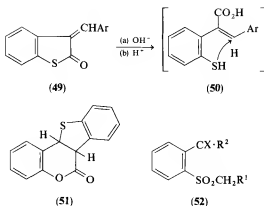
<sup>207</sup> A. Lüttringhaus and G. Creutzburg, German Patent 1,302,590 (1970) [*CA* **74**, 53572 (1971)].

<sup>208</sup> G. W. Stacy, D. L. Eck, and T. E. Wollner, *J. Org. Chem.*, **35**, 3495 (1970).

<sup>209</sup> R. A. Conley and N. D. Heindel, *J. Org. Chem.*, **41**, 3743 (1976).

<sup>210</sup> R. A. Conley and N. D. Heindel, *J. Org. Chem.*, **40**, 3169 (1975).

<sup>211</sup> B. Lamm and J. Simonet, *Acta Chem. Scand., Ser. B* **28**, 147 (1974).



$\text{Ph}(\text{CH}_2)_2\text{SO}_2^-$ . The *O*-methyl and *O*-benzyl derivatives of 2-methyl- or 2-phenylthioindoxyl 1,1-dioxide react with morpholine or piperidine, by successive addition and ring cleavage, to give the amides **52** ( $\text{R}^1 = \text{Me}$  or  $\text{Ph}$ ,  $\text{R}^2 = \text{piperidino}$  or  $\text{morpholino}$ ,  $\text{X} = \text{O}$ ); the *S*-benzyl derivative gives the appropriate thioamide **52** ( $\text{X} = \text{S}$ ).<sup>212</sup> In an analogous manner, 2-benzoyl-3-chlorobenzo[*b*]thiophene 1,1-dioxide reacts with 2-aminobenzenethiol, to give a 2-arylbenzothiazole ( $\text{aryl} = o\text{-C}_6\text{H}_4\cdot\text{SO}_2\text{CH}_2\text{COPh}$ ).<sup>213</sup>

### E. 2,3-DIDEHYDROBENZO[*b*]THIOPHENE (2,3-BENZO[*b*]THIOPHYNE)

The long-standing doubt over the existence of this hetaryne continues. The suggestion<sup>2</sup> that it may be involved in some of the nucleophilic displacement reactions of 2- and 3-bromobenzo[*b*]thiophene has now been refuted.<sup>214–216</sup> Heating bis(3-bromo-2-benzo[*b*]thienyl)mercury with tetraphenylcyclopentadienone at 275°C produces 1,2,3,4-tetraphenyldibenzo[*b*]thiophene (54%).<sup>217</sup> It is tempting to conclude that the reaction proceeds via the aryne. However, 3-bromobenzo[*b*]thiophene undergoes the same reaction, which might therefore proceed via a cycloaddition reaction of the

<sup>212</sup> K. Buggle, P. McManus, and D. O'Sullivan, *J. C. S. Perkin I*, 1136 (1978).

<sup>213</sup> W. Ried and J. B. Mavunkal, *Chem. Ber.* **111**, 1521 (1978).

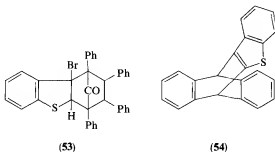
<sup>214</sup> M. G. Reinecke and T. A. Hollingworth, *J. Org. Chem.* **37**, 4257 (1972).

<sup>215</sup> D. A. de Bie, H. C. van der Plas, G. Geurtsen, and K. Nijdam, *Recl. Trav. Chim. Pays-Bas* **92**, 245 (1973).

<sup>216</sup> M. G. Reinecke, W. B. Mohr, H. W. Adickes, D. A. de Bie, H. C. van der Plas, and K. Nijdam, *J. Org. Chem.* **38**, 1365 (1973).

<sup>217</sup> G. Wittig and M. Rings, *Justus Liebigs Ann. Chem.* **719**, 127 (1968).

tetraphenylcyclopentadienone with the 2,3-double bond, followed by thermal elimination of HBr and CO from the adduct **53**. Recently, 3-aminobenzo[*b*]thiophene-2-carboxylic acid was diazotized and the  $\frac{1}{2}\text{HBF}_4$  salt was heated with anthracene, to give the heterotriptycene **54**.<sup>218</sup> This provides good, but not conclusive, evidence for the existence of 2,3-didehydrobenzo[*b*]thiophene.



It is believed that 2,3-thiophyne is formed when thiophene-2,3-dicarboxylic anhydride undergoes flash vacuum thermolysis. Trapping the intermediate with thiophene gives benzo[*b*]thiophene (59%) and sulfur.<sup>219</sup> The analogous reaction in the benzo[*b*]thiophene field seems not to have been attempted.

## IV. Derivatives of Benzo[*b*]thiophene

### A. SUBSTITUTION REACTIONS

This section is devoted to a brief survey of the substitution patterns in benzo[*b*]thiophene and its derivatives. Further discussion will be found in Section IV,B-P in which the derivative being substituted occurs.

#### 1. Electrophilic Substitution

a. *Reactivity Studies.* The last decade has witnessed an increasing interest in electrophilic substitution reactions: our call<sup>2</sup> for a careful re-examination of the earlier work, especially on isomer distribution, has been heeded, and there have been many kinetic studies. Electrophilic substitution in benzo[*b*]thiophene and its derivatives has been considered in terms of frontier orbitals (Section II,A).<sup>33,65,66</sup>

<sup>218</sup> M. G. Reinecke and H. H. Ballard, *Tetrahedron Lett.*, 4981 (1979).

<sup>219</sup> M. G. Reinecke and J. G. Newsom, *J. Am. Chem. Soc.* **98**, 3021 (1976).

The reactivity of benzo[b]thiophene has been considered in terms of the replacement constant  $\sigma^+$  (Note: terms used in correlation analysis are defined in Ref. 220). Most workers have concentrated on the 2- and 3-positions, for which  $\sigma^+$  values have been derived from the following reactions: protodesilylation,<sup>221</sup> protodetrithiation,<sup>222</sup> halogenation and acetylation,<sup>223</sup> solvolysis<sup>224</sup> and thermolysis<sup>225,226</sup> of 1-(substituted benzo[b]thienyl)ethyl acetates, and solvolysis of 1-(substituted benzo[b]thienyl)ethyl chlorides.<sup>227</sup> The last two reactions have also been used to provide  $\sigma^+$  values for all positions in the benzo[b]thiophene nucleus.<sup>226,227</sup> Plots of log (partial rate factor) against  $\rho$  for various electrophilic reactions of benzo[b]thiophene show curvature, implying a variable  $\sigma^+$  parameter.<sup>223</sup> The four-parameter Yukawa-Tsuno equation does not improve the correlation. Attempts have been made to explain the variable  $\sigma^+$  values in terms of a modified selectivity treatment.<sup>228</sup> The solvolytic rearrangement which accompanies the solvolysis of 2-(benzo[b]thienyl)ethyl tosylates has been studied, but the rates of this and related reactions do not correlate with either  $\sigma$  or  $\sigma^+$  values.<sup>229</sup> Data for the solvolysis of a series of substituted 1-(2-benzo[b]thienyl)ethyl *p*-nitrobenzoates have been correlated in terms of a new semiempirical mathematical model, which calculates the perturbational effects of substituents on aromatic reactivity.<sup>230</sup> Kinetic data for the base-catalyzed deuteration of the methyl groups in 2- and 3-methylbenzo[b]thiophene have been correlated with the  $\pi$ -electron density at C-2 and C-3, and used to estimate the  $\sigma^-$  and  $\sigma^0$  values of the heteroaryl substituent.<sup>231</sup>

With one exception,<sup>225</sup> the above results all confirmed the well-established fact that the 3-position is more reactive than the 2-position toward electrophiles. The  $\sigma^+$  values from the solvolysis of 1-(benzo[b]thienyl)ethyl chlorides<sup>227</sup> and from the thermolysis of the corresponding acetates,<sup>226</sup> lead to the same positional order of reactivity in the benzo[b]thiophene

<sup>220</sup> O. Exner, in "Correlation Analysis in Chemistry" (N. B. Chapman and J. Shorter, eds.), Chapter 10. Plenum, New York, 1978.

<sup>221</sup> C. Eaborn and J. A. Sperry, *J. Chem. Soc.*, 4921 (1961).

<sup>222</sup> R. Baker, C. Eaborn, and R. Taylor, *J. C. S., Perkin II*, 97 (1972).

<sup>223</sup> S. Clementi, P. Linda, and C. D. Johnson, *J. C. S. Perkin II*, 1250 (1973).

<sup>224</sup> E. A. Hill, M. L. Gross, M. Stasiewicz, and M. Manion, *J. Am. Chem. Soc.* **91**, 7381 (1969).

<sup>225</sup> G. G. Smith and J. A. Kirby, *J. Heterocycl. Chem.* **8**, 1101 (1971).

<sup>226</sup> H. B. Amin and R. Taylor, *J. C. S. Perkin II*, 1053 (1978).

<sup>227</sup> D. S. Noyce and D. A. Forsyth, *J. Org. Chem.* **39**, 2828 (1974).

<sup>228</sup> A. A. Humfray and R. L. Bruce, *J. Org. Chem.* **44**, 724 (1979).

<sup>229</sup> D. S. Noyce and R. L. Castenson, *J. Am. Chem. Soc.* **95**, 1247 (1973).

<sup>230</sup> D. A. Forsyth, *J. Am. Chem. Soc.* **95**, 3594 (1973).

<sup>231</sup> N. N. Zatsepina, I. F. Tupitsyn, Yu. L. Kaminskii, and N. S. Kolodina, *Feakts. Sposobn. Org. Soedin.* **6**, 766 (1969).

molecule, viz.,  $3 > 2 > 6 > 5 > 4 > 7$ , but the actual values differ markedly for some positions (e.g., the 7-position is deactivated in the thermolysis reaction, but activated in the solvolysis reaction). The order of reactivity is explained simply in terms of the number and relative stabilities of the canonical forms used to represent the structure of the transition state. The recently demonstrated<sup>232</sup> ability of sulfur to stabilize an adjacent cation also provides a rationalization for predominant 3-substitution. From a study of the literature, Royer *et al.* predicted that the order of reactivity of the various positions toward electrophiles should be  $3 \approx 2 > 6 \approx 5 > 4$  or  $7$ .<sup>233</sup> A careful study of the nitration of benzo[b]thiophene in AcOH has shown that the following mononitro isomers are formed: 3- (56%)  $\gg$  4- (13%) 2- (12%)  $\approx$  7- (11%)  $\approx$  6- (10%)  $\gg$  5- (0%).<sup>234</sup>

Electrophilic substitution in benzo[b]thiophene has been compared with that in thiophene, furan, and benzo[b]furan.<sup>235</sup> The fusion of a thiophene ring with a benzene ring lowers the reactivity of the 2-position in thiophene by a factor of 10 and raises that of the 3-position by a factor of 180.<sup>222</sup> The general order of relative reactivities is: 3-position in thiophene  $\approx$  3-position in furan  $<$  3-position in benzo[b]furan  $\approx$  2-position in benzo[b]thiophene  $<$  3-position in benzo[b]thiophene  $\approx$  2-position in benzo[b]furan  $\ll$  2-position in thiophene  $\ll$  2-position in furan.<sup>236</sup>

b. *Substitution Patterns.* The main patterns of electrophilic substitution have previously been described.<sup>2</sup> *t*-Butylation of benzo[b]thiophene with 2-methylpropene-PPA or *t*-Bu-OH—H<sub>2</sub>SO<sub>4</sub> gives a mixture of the 2- (22 and 6%) and 3-*t*-butyl isomers (71 and 89%),<sup>74</sup> and not just the 3-isomer as was previously thought.<sup>2</sup> Allylation under neutral conditions (allyl iodide—Cl<sub>3</sub>CCO<sub>2</sub>Ag) is said, however, to give entirely the 3-isomer.<sup>87,237</sup> Mercuration of benzo[b]thiophenes is only possible if there is a free thiophene position.<sup>238</sup> In the presence of CF<sub>3</sub>CO<sub>2</sub>H, benzo[b]thiophene is substituted by quinazoline or its 2-methyl derivative, to give the salts **55** [R = H, Ar = 2- or 3-benzo[b]thienyl (2-:3- = 1:7) and R = Me, Ar = 2- or 3-benzo[b]thienyl (2-:3- = 1:1), respectively].<sup>239</sup>

<sup>232</sup> F. Bernardi, A. Mangini, N. D. Epiotis, J. R. Larson, and S. Shaik, *J. Am. Chem. Soc.* **99**, 7465 (1977).

<sup>233</sup> O. Chalvet, R. Royer, and P. Demerseman, *Bull. Soc. Chim. Fr.*, 1483 (1970).

<sup>234</sup> K. J. Armstrong, M. Martin-Smith, N. M. D. Brown, G. C. Brophy, and S. Sternhell, *J. Chem. Soc. C*, 1766 (1969).

<sup>235</sup> G. Marino, *Adv. Heterocycl. Chem.* **13**, 235 (1971).

<sup>236</sup> S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc. B*, 79 (1971).

<sup>237</sup> A. V. Anisimov, Yu. N. Luzikov, V. M. Nikolaeva, and E. A. Viktorova, *Zh. Org. Khim.* **15**, 172 (1979).

<sup>238</sup> I. M. Nasyrov and I. U. Numanov, *Dokl. Akad. Nauk Tadzh. SSR* **11**, 44 (1968).

<sup>239</sup> W. P. K. Girke, *Chem. Ber.* **112**, 1348 (1979).





There is now abundant evidence that benzo[*b*]thiophenes containing a strongly electron-withdrawing 3-substituent are nitrated only in the benzenoid ring.<sup>234,240,241</sup> In contrast, a 2-electron-withdrawing group gives some of the 3-nitro isomer,<sup>242</sup> and 2-chlorobenzo[*b*]thiophene is brominated entirely in the 3-position.<sup>243</sup>

Substitution reactions of some 4- and 6-substituted benzo[*b*]thiophenes have now been examined. Generally, these give the 2- and/or 3- derivative,<sup>244,245</sup> except for strongly activating groups such as 6-OH, 6-NHAc, and 4-OMe, which also substitute in the 7-position<sup>244,246,247</sup>; 4-OH substitutes preferentially in the 5-position.<sup>248</sup> There are only two examples of substitution reactions on a 7-substituted benzo[*b*]thiophene. Predictably, the 7-hydroxy-3-methyl derivative is substituted mainly in the 4- and 6-positions<sup>249</sup>; the 7-chloro-3-methyl derivative undergoes 2-substitution.<sup>250</sup>

*c. Less Common Substitution Reactions.* With modern chromatographic techniques, it is now possible to isolate by-products which previously went unnoticed. The replacement of the following ring substituents by an electrophile has been observed: 3-Br,<sup>243,251</sup> 3-*t*-Bu,<sup>74</sup> 3-CO<sub>2</sub>H,<sup>234,241</sup> 2-Ac,<sup>252</sup> 3-Ac, and 3-CHO.<sup>240</sup> In the nitration of 2,3-dibromobenzo[*b*]thiophene, one of the products is 2,3,6-tribromobenzo[*b*]thiophene, formed by

<sup>240</sup> G. C. Brophy, S. Sternhell, N. M. D. Brown, I. Brown, K. J. Armstrong, and M. Martin-Smith, *J. Chem. Soc. C*, 933 (1970).

<sup>241</sup> I. Brown, S. T. Reid, N. M. D. Brown, K. J. Armstrong, M. Martin-Smith, W. E. Sneider, G. C. Brophy, and S. Sternhell, *J. Chem. Soc. C*, 2755 (1969).

<sup>242</sup> J. Cooper and R. M. Scrowston, *J. Chem. Soc. C*, 3405 (1971).

<sup>243</sup> R. P. Dickinson, B. Iddon, and R. G. Sommerville, *Int. J. Sulfur Chem.* **8**, 233 (1973).

<sup>244</sup> P. D. Clark, K. Clarke, R. M. Scrowston, and T. M. Sutton, *J. Chem. Res. (S)*, 10; (*M*), 368 (1978).

<sup>245</sup> E. Campaigne, A. Dinner, and E. S. Neiss, *J. Heterocycl. Chem.* **7**, 695 (1970).

<sup>246</sup> E. Campaigne, A. Dinner, and M. Haseman, *J. Heterocycl. Chem.* **8**, 755 (1971).

<sup>247</sup> K. Clarke, R. M. Scrowston, and T. M. Sutton, *J. C. S. Perkin I*, 623 (1973).

<sup>248</sup> K. Clarke, R. M. Scrowston, and T. M. Sutton, *J. C. S. Perkin I*, 1196 (1973).

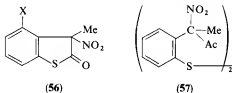
<sup>249</sup> N. B. Chapman, K. Clarke, and A. Manolis, *J. C. S. Perkin I*, 2593 (1972).

<sup>250</sup> N. B. Chapman, K. Clarke, and A. Manolis, *J. C. S. Perkin I*, 1404 (1972).

<sup>251</sup> J. Cooper and R. M. Scrowston, *J. C. S. Perkin I*, 265 (1972).

<sup>252</sup> R. Royer, P. Demerseman, and S. Risse, *Bull. Soc. Chim. Fr.*, 1691 (1974).

attack of an expelled  $\text{Br}^+$  ion.<sup>253</sup> Similarly, 2,3-dibromobenzo[b]thiophene is formed during the chlorination of 3-bromobenzo[b]thiophene.<sup>243</sup> Side-chain substitution is sometimes observed under conditions which normally lead to nuclear substitution, e.g., in the nitration of 2,3-dimethyl-<sup>251</sup> and 7-chloro-3-methylbenzo[b]thiophene<sup>250</sup> and in the bromination of 4-chloro-3-methylbenzo[b]thiophene.<sup>244</sup> Ipso substitution is observed in the nitration of 2-bromo-<sup>254</sup> and 4-chloro-3-methylbenzo[b]thiophene,<sup>244</sup> giving the thiooxindole derivatives **56** ( $\text{X} = \text{H}$  and  $\text{Cl}$ , respectively). The ring-opened product **57** is formed (10%) in the nitration of 2,3-dimethylbenzo[b]thiophene.<sup>251</sup> The formation of furoxans can be an important competing reaction in the nitration of 3-acetylbenzo[b]thiophenes.<sup>240,252</sup>



## 2. Base-Catalyzed Exchange Reactions

Base-catalyzed proton-deuterium exchange at H-2 and H-3 in benzo[b]-thiophene has been extensively studied,<sup>255-258</sup> but the results are contradictory. H-2 is replaced faster than H-3 in benzo[b]thiophene, and faster than H-2 in benzo[b]furan. The marked ability of the sulfur atom to stabilize the 2-carbanion has been discussed in terms of *d*-orbital participation, electronegativity, and polarization phenomena, but no convincing conclusions have yet been reached.

The ionization of the H-2 and H-3 bonds in 3-methyl- and 2-methylbenzo[b]thiophene ( $\text{ArH}$ ) has been measured by polarographic reduction of the corresponding  $\text{Ar}_2\text{Hg}$  compounds; the  $\text{pK}_a$  values are approximately 35 and 36, respectively.<sup>259</sup> Kinetic results from the polarographic study

<sup>253</sup> J. Cooper, D. F. Ewing, R. M. Scrowston, and R. Westwood, *J. Chem. Soc. C*, 1949 (1970).

<sup>254</sup> J. Cooper and R. M. Scrowston, *J. Chem. Soc. C*, 3052 (1971).

<sup>255</sup> N. N. Zatspeina, Yu. L. Kaminskii, and I. F. Tupitsyn, *Reakts. Sposobn. Org. Soedin*, **6**, 753 (1969).

<sup>256</sup> O. Attanasi, *J. Heterocycl. Chem.*, **14**, 95 (1977).

<sup>257</sup> T. A. Yakushina, I. O. Shapiro, E. N. Zvyagintseva, V. P. Litvinov, S. Ozolins, Ya. L. Gol'dfarb, and A. I. Shatenshtein, *Zh. Obshch. Khim.*, **41**, 1930 (1971) [*CA* **76**, 24481 (1972)].

<sup>258</sup> O. Attanasi, P. Battistoni, and G. Fava, *Phosphorus Sulfur*, **5**, 305 (1979).

<sup>259</sup> K. P. Butin, L. G. Yudin, A. I. Pavlyuchenko, I. P. Beletskaya, and A. N. Kost, *J. Org. Chem. USSR (Engl. Transl.)*, **7**, 2686 (1971).

correlate favorably with those obtained from base-catalyzed H-D exchange reactions.

The relative equilibrium ion-pair acidity of benzo[*b*]thiophene toward cesium cyclohexylamide in cyclohexylamine has been determined; the  $pK_a$  value for the 2-position relative to 9-phenylfluorene (= 18.49) is found to be 37.05.<sup>260</sup> Surprisingly, the  $pK_a$  value for the 2-position in benzo[*b*]furan is lower than this, showing that, in contrast to the results just described, thermodynamic acidity seems to be enhanced more by an oxygen atom than by a sulfur atom.

### 3. Other Substitution Reactions

Homolytic phenylation of benzo[*b*]thiophene, using phenyl radicals generated by the thermal decomposition of *N*-nitrosoacetanilide, takes place in all available positions, each showing comparable reactivity.<sup>261</sup> Unusually, benzo[*b*]thiophene undergoes arylation when treated with a 2,4-dinitrobenzenediazonium salt under *acidic* conditions, to give a mixture of 2-(2,4-dinitrophenyl)benzo[*b*]thiophene and the 2,3-bisaryl compound.<sup>262</sup> In contrast, under similar conditions, 2- and 3-methylbenzo[*b*]thiophene couple with the 2,4-dinitrobenzenediazonium ion in the vacant thiophene position, to give an azo dye.<sup>263</sup> 3-Benzo[*b*]thienyl radicals, generated by photolysis of the 3-iodo compound, undergo substitution in the ortho, meta, and para positions of anisole, cumene, and methyl benzoate.<sup>264</sup>

Benzo[*b*]thiophene undergoes nitrene insertion with phthalimidonitrene, to give 3-(phthalimidoamino)benzo[*b*]thiophene.<sup>265</sup>

## B. HYDROBENZO[*b*]THIOPHENES

In previous reviews, thiooxindole (benzo[*b*]thiophen-2(3*H*)-one) and thioindoxyl (benzo[*b*]thiophen-3(2*H*)-one) have been discussed in the sections dealing with hydroxybenzo[*b*]thiophenes.<sup>1,2</sup> Because they are now known to exist mainly as the oxo tautomers, tradition has been broken, and they are here discussed as oxo derivatives of 2,3-dihydrobenzo[*b*]thiophene. To prevent confusion, a few 2-substituted thioindoxyls, which are known to be predominantly enolic, are referred to as derivatives of the oxo

<sup>260</sup> A. Streitwieser and P. J. Scannon, *J. Am. Chem. Soc.* **95**, 6273 (1973).

<sup>261</sup> P. Spagnolo, M. Tiecco, A. Tundo, and G. Martelli, *J. C. S. Perkin I*, 556 (1972).

<sup>262</sup> M. Bartle, S. T. Gore, R. K. Mackie, and J. M. Tedder, *J. C. S. Perkin I*, 1636 (1976).

<sup>263</sup> S. T. Gore, R. K. Mackie, and J. M. Tedder, *J. C. S. Perkin I*, 1639 (1976).

<sup>264</sup> L. Benati, G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. B*, 472 (1969).

<sup>265</sup> D. W. Jones, *J. C. S. Perkin I*, 1150 (1976).

form. For simplicity, the trivial names, thiooxindole and thioindoxyl, are reluctantly retained.

### 1. Thiooxindoles [Benzo[*b*]thiophen-2(3H)-ones]

Thiooxindole and its ring-substituted derivatives are conveniently obtained by treatment of the appropriate 2-benzo[*b*]thienyllithium with *n*-butyl borate, followed by oxidation of the resulting cyclotriboroxane with  $\text{H}_2\text{O}_2$ .<sup>206,254,266</sup> Alternatively, the 2-lithio derivative may be treated successively with  $\text{MgBr}_2$  and  $\text{PhCO}_3\text{-}t\text{-Bu}$ , to give the 2-*O*-*t*-Bu derivative, acid treatment of which give thiooxindole.<sup>267</sup>

2-Methoxybenzo[*b*]thiophene may be obtained (90%) by methylation of thiooxindole with  $\text{Me}_2\text{SO}_4\text{-NaH}$  in hexamethylphosphoric triamide (HMPA)<sup>206</sup>; alkylation by other reagents gives a complex mixture of *C*- and *O*-alkyl derivatives and ring-opened products.<sup>267</sup>

Thiooxindole reacts under appropriate conditions with the following reagents, to give the condensation products **58**: aryl aldehydes (**58**,  $\text{X} = \text{CHAr}$ )<sup>209,210</sup>; ortho esters,  $\text{RCH}_2\text{C}(\text{OEt})_3$  [**58**,  $\text{X} = \text{C}(\text{OEt})\cdot\text{CH}_2\text{R}$ ]<sup>268</sup>; 1,1-dimethoxyethene [**58**,  $\text{X} = \text{CMe}(\text{OMe})$  (*sic*)]<sup>269</sup>; and ethereal diazo-methane (**58**,  $\text{X} = \text{N}\cdot\text{NHMe}$ ).<sup>270</sup>



Photolysis of thiooxindole gives the intermediate **59**, which has been trapped as its cycloadduct with *N*-phenylmaleimide.<sup>271</sup> Acid-catalyzed decomposition of 3-diazothiooxindole (**58**,  $\text{X} = \text{N}_2$ ) in the presence of MeOH gives 3-methoxythiooxindole. However, photolysis in methanol gives the benzothiete derivative **60** ( $\text{X} = \text{H}$ ,  $\text{Y} = \text{CO}_2\text{Me}$ ).<sup>272</sup> The latter reaction proceeds via the ketene **60** ( $\text{XY} = \text{:C=O}$ ), the existence of which has been confirmed by variable-temperature PE spectroscopy, following the pyrolysis of the diazo compound **58** ( $\text{X} = \text{N}_2$ ) at  $350^\circ\text{C}$  and 0.05 mm Hg.<sup>273</sup> The

<sup>266</sup> W. C. Lumma, G. A. Dutra, and C. A. Voeker, *J. Org. Chem.* **35**, 3442 (1970).

<sup>267</sup> N. O. Vesterager, E. B. Pedersen, and S.-O. Lawesson, *Tetrahedron* **29**, 321 (1973).

<sup>268</sup> H. Wolfers, U. Kraatz, and F. Korte, *Chem. Ber.* **109**, 1061 (1976).

<sup>269</sup> O. L. Chapman, C. L. McIntosh, and J. C. Clardy, *J. C. S. Chem. Commun.*, 384 (1971).

<sup>270</sup> R. Schmichen, *Tetrahedron Lett.*, 4995 (1969).

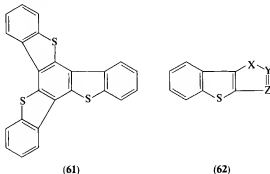
<sup>271</sup> G. Jacqmin, J. Nasielski, G. Billy, and M. Remy, *Tetrahedron Lett.*, 3655 (1973).

<sup>272</sup> E. Voigt and H. Meier, *Angew. Chem., Int. Ed. Engl.* **15**, 117 (1976); *Chem. Ber.* **110**, 2242 (1977).

<sup>273</sup> R. Schulz and A. Schweig, *Tetrahedron Lett.* **21**, 343 (1980).

parent benzothiete **60** ( $X = Y = H$ ) is obtained from thiooxindole by flash vacuum pyrolysis at 700°C and 0.1 mm Hg.<sup>273</sup>

The conversion of thiooxindole into 2-aminobenzo[*b*]thiophene derivatives is mentioned in Section IV.F.1.a. Heating thiooxindole under pressure gives mainly the polycyclic derivative **61**.<sup>274</sup>



## 2. Thioindoxyls [*Benzo*[*b*]thiophen-3(2H)-ones]

$\omega$ -Diazo-2-(methylthio)acetophenone, which is readily prepared from 2-mercaptobenzoic acid, affords thioindoxyl (73%) on treatment with a proton donor (e.g., ethanolic thiourea).<sup>275</sup> The nitro group in methyl 2-nitrobenzoate (and its ring-substituted derivatives) is displaced by  $SCH_2CO_2Me$  in DMF in the presence of LiOH, and the resulting diester undergoes spontaneous cyclization, to give 2-methoxycarbonylthioindoxyl.<sup>276</sup>

There has been interest in the functionalization of thioindoxyl in the 2-position. 2-Arylidene derivatives are readily formed by reaction with  $ArCHO$ <sup>2,85</sup>; treatment of thioindoxyl with  $CS_2-NaOH$ , followed by methylation, gives mainly the 2-CS·SMe derivative<sup>277</sup>; reductive acetylation of the 2-nitroso derivative gives 2-acetamidothioindoxyl<sup>278</sup>; and reaction of thioindoxyl with  $HCN-HCl$  gives the 2-carboxaldehyde, via the imine.<sup>279</sup>

<sup>274</sup> R. Proetzsch, D. Bieniek, and F. Korte, *Z. Naturforsch., Teil B: Anorg. Chem., Org. Chem.* **31**, 529 (1976).

<sup>275</sup> W. Hampel and J. Friedrich, *Z. Chem.* **10**, 343 (1970).

<sup>276</sup> J. R. Beck, *J. Org. Chem.* **38**, 4086 (1973).

<sup>277</sup> Y. Tominaga, Y. Morita, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull.* **23**, 2390 (1975).

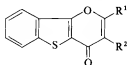
<sup>278</sup> V. G. Zhiryakov and P. I. Abramenko, *Zh. Vses. Khim. O-va*, **15**, 587 (1970) [*CA* **74**, 13040 (1971)].

<sup>279</sup> V. P. Litvinov, L. N. Smirnov, Ya. L. Gol'dfarb, N. N. Petukhova, and E. G. Ostapenko, *Khim. Geterotsikl. Soedin.*, 480 (1975).

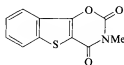
Under conventional conditions for forming Mannich bases, thioindoxyl gives complex products, but treatment of 5-methylthioindoxyl with *N,N*-dialkylmethyleneimmonium salts ( $\text{CH}_2=\text{NR}^1\text{R}^2\text{Cl}^-$ ) readily gives the corresponding  $2\text{-CH}_2\text{NR}^1\text{R}^2$  derivative.<sup>280</sup>

Thioindoxyls are useful precursors of the tricyclic systems **62**: heating 2-acetamidothioindoxyl gives the oxazole **62** ( $\text{X} = \text{O}$ ,  $\text{Y} = \text{CMe}$ ,  $\text{Z} = \text{N}$ )<sup>278</sup>; a 2-arylthioindoxyl reacts with phenylhydrazine (1 mol equiv) at the aryl carbonyl group, and the resulting phenylhydrazone is cyclized by AcOH, to give the pyrazole **62** ( $\text{X} = \text{NPh}$ ,  $\text{Y} = \text{N}$ ,  $\text{Z} = \text{CAr}$ )<sup>281</sup>; 2-methoxycarbonylthioindoxyl is *O*-alkylated by  $\text{KO}-t\text{-Bu}/\text{ClCH}_2\text{R}$  ( $\text{R} = \text{CO}_2\text{Me}$ ,  $\text{COMe}$ , or  $\text{CN}$ ), then the product undergoes Dieckmann cyclization to give the furans **62** ( $\text{X} = \text{O}$ ,  $\text{Y} = \text{CR}$ ,  $\text{Z} = \text{C}\cdot\text{OH}$ )<sup>282</sup>; and thioindoxyl semicarbazone cyclizes to the thiadiazole **62** ( $\text{XYZ} = \text{N:N}\cdot\text{S}$ ), when treated with  $\text{SOCl}_2$ .<sup>283</sup>

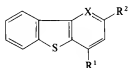
The benzothienopyrans **63** can be obtained from 2-acetyl- or 2-benzoylthioindoxyl: treatment of the former with  $\text{NaOEt}-(\text{CO}_2\text{Et})_2$  gives **63** ( $\text{R}^1 = \text{CO}_2\text{Et}$ ,  $\text{R}^2 = \text{H}$ )<sup>284</sup>; heating the 2-benzoyl derivative with PPA gives **63** ( $\text{R}^1\text{R}^2 = \text{C}_6\text{H}_4\text{-}o$ ).<sup>285</sup> 2-Methoxycarbonylthioindoxyl reacts with  $\text{MeNCO}-\text{NEt}_3$ , to give the benzothienooxazine **64**.<sup>282</sup> With the  $\alpha,\beta$ -unsaturated ketones,  $\text{R}^2\text{COCH}=\text{CHR}^1$ , in the presence of  $\text{HClO}_4$ , thioindoxyl gives the pyrylium salts **65** ( $\text{X} = \text{O}$ ); these give the pyridine derivatives **65** ( $\text{X} = \text{N}$ ) when treated with  $\text{NH}_4\text{OAc}$ .<sup>286</sup>



(63)



(64)



(65)



(66)

<sup>280</sup> M. Schaefer, J. Weber, and P. Faller, *Bull. Soc. Chim. Fr.*, Pt. 2, 241 (1978).

<sup>281</sup> S. B. Awad and N. F. Abdul-Malik, *Aust. J. Chem.*, **28**, 601 (1975).

<sup>282</sup> J. R. Beck, *J. Heterocycl. Chem.*, **12**, 1037 (1975).

<sup>283</sup> H. Meier, G. Trickes, E. Laping, and U. Merkle, *Chem. Ber.*, **113**, 183 (1980).

<sup>284</sup> J. B. Wright and H. G. Johnson, *J. Med. Chem.*, **16**, 861 (1973).

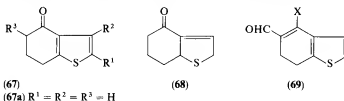
<sup>285</sup> K. Görlitzer, *Arch. Pharm. (Weinheim, Ger.)*, **307**, 523 (1974).

<sup>286</sup> G. N. Dorofeenko, V. I. Volbushko, V. I. Dulenka, and E. N. Kornilova, *Khim. Geterotsikl. Soedin.*, 1181 (1976).

Conventional base-catalyzed alkylation of thioindoxyl 1,1-dioxide with "unreactive" alkyl halides does not proceed cleanly; the products **66** ( $X = H$ ,  $Y = \text{alkyl}$ ) are better obtained by alkylation in the presence of the sterically hindered base, diisopropylethylamine, in propan-2-ol.<sup>287</sup> Thioindoxyl 1,1-dioxide reacts as expected in the Michael reaction; e.g., with acrylonitrile, **66** ( $X = H$ ,  $Y = \text{CH}_2\text{CH}_2\text{CN}$ ) is obtained. Treatment of thioindoxyl 1,1-dioxide with *p*-toluenesulfonyl azide<sup>288</sup> or 2-azido-3-ethylbenzothiazolium tetrafluoroborate<sup>289</sup> affords the diazo compound **66** ( $XY = \text{N}_2$ ), which gives the 2-methoxy compound **66** ( $X = H$ ,  $Y = \text{OMe}$ ) when treated with  $\text{MeOH}-\text{Cu}-\text{HClO}_4$ .<sup>288</sup>

### 3. 6,7-Dihydrobenzo[b]thiophen-4(5H)-one (**67a**)

Ketone **67a** is formed directly by cyclization of  $\gamma$ -(2-thienyl)butyric acid with  $\text{PPA}-\text{Ac}_2\text{O}$ <sup>290,291</sup>; under these conditions, the 2-acetyl derivative **67** ( $R^1 = \text{Ac}$ ,  $R^2 = R^3 = H$ ) is formed as a by-product.<sup>148,291</sup> Similar attempts to prepare the 3-methyl analog **67** ( $R^1 = R^3 = H$ ,  $R^2 = \text{Me}$ ) gave the 2-acetyl derivative **67** ( $R^1 = \text{Ac}$ ,  $R^2 = \text{Me}$ ,  $R^3 = H$ ) in high yield, even under mild conditions.<sup>291</sup> Ketone **67a** is probably best prepared by dehydrogenation of



**68** with chloranil; **68** is obtained by acid-catalyzed cyclization of the Michael adduct from cyclohex-2-enone and  $(\text{EtO})_2\text{CHCH}_2\text{SH}$ .<sup>292</sup> Substituted 3-mercaptocyclohexanones react directly with the 1,2-dicarbonyl compounds,  $R^1\text{COCOR}^2$ , in the presence of an aromatic sulfonic acid, to give the 2,3-disubstituted compounds **67** ( $R^3 = H$  or 6-Me or 7-Me).<sup>293</sup>

Bromination of **67a** in acetic acid gives first the 2-bromo, then the 2,3-dibromo derivative.<sup>290</sup> The 2-iodo derivative is obtained by iodination of

<sup>287</sup> J. G. Lombardino, *J. Org. Chem.* **33**, 3938 (1968).

<sup>288</sup> G. Ferdinand, W. Jeblick, and K. Schank, *Justus Liebigs Ann. Chem.*, 1713 (1976).

<sup>289</sup> H. Balli, R. Löw, V. Müller, H. Rempfler, and A. Sezen-Gezgin, *Helv. Chim. Acta* **61**, 97 (1978).

<sup>290</sup> D. T. Drewry and R. M. Scrowston, *J. Chem. Soc. C*, 2750 (1969).

<sup>291</sup> C. M. Asprou, J. S. A. Brunskill, H. Jeffrey, and A. De, *J. Heterocycl. Chem.* **17**, 87 (1980).

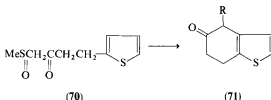
<sup>292</sup> R. P. Napier, H. A. Kaufman, P. R. Driscoll, L. A. Glick, C.-C. Chu, and H. M. Foster, *J. Heterocycl. Chem.* **7**, 393 (1970).

<sup>293</sup> R. P. Napier and C.-C. Chu, *Int. J. Sulfur Chem., Part A* **1**, 62 (1971).

**67a** with  $\text{HgO-I}_2$ .<sup>294</sup> Bromination of **67a** in ether gives a mixture of the 5-bromo (79%) and the 5,5- (5%) and 2,5-dibromo compounds (10%).<sup>290</sup> Vilsmeier-Haack formylation of **67a** with *N*-methyl formanilide- $\text{POCl}_3$  gives only 5% of the expected aldehyde **69** ( $\text{X} = \text{Cl}$ ); the other products are the 5-hydroxymethylene derivative **67** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{:CHOH}$ ) (29%), the aldehyde **69** ( $\text{X} = \text{NMe}\cdot\text{Ph}$ ) (38%) and its  $\text{HCl}$  salt (19%), and the 2-aldehyde **67** ( $\text{R}^1 = \text{CHO}$ ,  $\text{R}^2 = \text{R}^3 = \text{H}$ ) (4.5%).<sup>290</sup>

The 5-bromo compound **67** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Br}$ ), the 5-hydroxymethylene compound **67** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{:CHOH}$ ), and the aldehyde **69** ( $\text{X} = \text{Cl}$ ) have been used to prepare tricyclic systems, by treating them with an appropriate nucleophile.<sup>290, 295-297</sup>

#### 4. 6,7-Dihydrobenzo[b]thiophen-5(4H)-one (**71**; $\text{R} = \text{H}$ )



Acid-catalyzed cyclization of the  $\beta$ -ketosulfoxide **70** gives the methylthio compound **71** ( $\text{R} = \text{SMe}$ ),<sup>298</sup> which undergoes selective dehydrosulfurization with Raney nickel in acetone, to give the ketone **71** ( $\text{R} = \text{H}$ ).<sup>299</sup>

#### 5. 4,5-Dihydrobenzo[b]thiophen-7(6H)-one (**72**; $\text{R} = \text{H}$ )



<sup>294</sup> J.-P. Conjat, P. Cagniant, D. Cagniant, and M. Mirjolet, *Tetrahedron Lett.*, 2885 (1975).

<sup>295</sup> W. A. Remers, G. J. Gibbs, J. F. Poletto, and M. J. Weiss, *J. Med. Chem.* **14**, 1127 (1971).

<sup>296</sup> A. Ricci, D. Balucani, C. Rossi, and A. Croisy, *Boll. Sci. Fac. Chim. Ind. Bologna* **27**, 279 (1969) [*CA* **72**, 111328 (1970)].

<sup>297</sup> P. Cagniant and G. Kirsch, *C. R. Acad. Sci., Ser. C* **281**, 393 (1975).

<sup>298</sup> Y. Oikawa and O. Yonemitsu, *J. Org. Chem.* **41**, 1118 (1976).

<sup>299</sup> H. Takahata, M. Hara, A. Tomiguchi, T. Yamazaki, and R. N. Castle, *J. Heterocycl. Chem.* **17**, 403 (1980).



This ketone may be obtained (80%) by direct oxidation of 4,5,6,7-tetrahydrobenzo[b]thiophene with a Ce(IV) salt<sup>294</sup> or by cyclization of the rather inaccessible  $\gamma$ -(3-thienyl)butyric acid.<sup>300</sup>  $\gamma$ -(2,5-Di-*t*-butyl-3-thienyl)-butyric acid is cyclized by PPA with the expulsion of the 2-*t*-Bu group, to give **72** (R = *t*-Bu).<sup>301</sup> 2-Acetylthiophene reacts with but-2-ene in the presence of a Mn(III) salt, to give the 4,5-dimethyl derivative of **72** (R = H).<sup>302</sup>

Ketone **72** (R = H) is iodinated in the 3-position by  $I_2$ -HIO<sub>3</sub>-H<sub>2</sub>SO<sub>4</sub>.<sup>294</sup> Attempts to prepare 4,5-dihydrobenzo[b]thiophene by dehydration of the alcohol obtained from ketone **72** (R = H) were unsuccessful.<sup>300</sup> However, this labile alkene has been obtained (72%) by vacuum pyrolysis of 1-(2-thienyl)buta-1,3-diene.<sup>303</sup>

### 6. 2,3-Dihydrobenzo[b]thiophene

2,3-Dihydrobenzo[b]thiophene may be obtained by reduction of benzo[b]thiophene (Section III,A,1) by treating 2-*o*-(benzylthio)phenylethanol with SOCl<sub>2</sub>-pyridine (91%),<sup>208</sup> and by cyclization of *o*-(methylthio)phenylcarbene at 250°C (45%); the last procedure is mainly of academic interest.<sup>304</sup> Substituted phenyl vinyl sulfides undergo photocyclization to the expected 2,3-dihydrobenzo[b]thiophene; the reaction proceeds via an excited triplet state.<sup>305</sup> *o*-Allylthiophenol, an intermediate in the thio-Claisen rearrangement of allyl phenyl sulfide, cyclizes spontaneously to give 2,3-dihydro-2-methylbenzo[b]thiophene.<sup>306</sup>

2,3-Dihydrobenzo[b]thiophenes are dehydrogenated to the parent benzo[b]thiophene with trityl tetrafluoroborate<sup>307</sup> or hot activated carbon.<sup>308</sup> 2,3-Dihydrobenzo[b]thiophene and its 2- and 3-methyl derivatives are brominated in the 2-position by Br<sub>2</sub>-CCl<sub>4</sub> at 50°C.<sup>309</sup>

<sup>300</sup> P. Cagniant, G. Merle, and D. Cagniant, *Bull. Soc. Chim. Fr.*, 322 (1970).

<sup>301</sup> G. Muraro, D. Cagniant, and P. Cagniant, *C. R. Acad. Sci., Ser. C* **274**, 201 (1972).

<sup>302</sup> E. I. Heiba and R. M. Dessau, *J. Am. Chem. Soc.* **94**, 2888 (1972).

<sup>303</sup> B. I. Rosen and W. P. Weber, *Tetrahedron Lett.*, 151 (1977).

<sup>304</sup> W. D. Crow and H. McNab, *Aust. J. Chem.* **32**, 99 (1979).

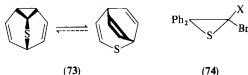
<sup>305</sup> T. Wolff, *J. Photochem.* **11**, 215 (1979).

<sup>306</sup> H. Kwart and J. L. Schwartz, *J. Org. Chem.* **39**, 1575 (1974).

<sup>307</sup> A. V. Anisimov, L. M. Kedik, L. P. Ermolenko, and E. A. Viktorova, *Neftekhimiya* **17**, 148 (1977) [*CA* **86**, 171199 (1977)].

<sup>308</sup> M. V. Vagabov, S. K. Dzhamalov, E. A. Karakhanov, and E. A. Viktorova, *Vestn. Mosk. Univ., Khim.*, 201 (1978) [*CA* **89**, 90152 (1978)].

<sup>309</sup> I. U. Numanov, S. S. Dzhalolov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **13**, 31 (1970).

7. *cis*-3*a*,7*a*-Dihydrobenzo[b]thiophene

This unusual bridgehead dihydro compound is obtained (75%) when the mixture of isomeric sulfides **73** is heated to 80°C.<sup>310</sup>

## C. DERIVATIVES WITH A HYDROCARBON SIDE CHAIN

1. *Preparation of Arylbenzo[b]thiophenes*

Attention has been centered mainly on the preparation of 2- and 3-aryl and 2,3-diaryl derivatives. 2- and 3-Phenylbenzo[b]thiophene are obtained by heating  $\text{PhCH}_2\text{Br}$  and  $\text{Ph}_2\text{CHCHCl}_2$ , respectively, with sulfur at 240°C.<sup>311,312</sup> Diphenylethyne reacts with ethereal sulfur dichloride at 20°C, to give 3-chloro-2-phenylbenzo[b]thiophene (90%).<sup>313</sup> Heating the thiirane **74** (X = Cl or Br), formed by reaction of thiobenzophenone with  $\text{PhHgCCl}_2\cdot\text{Br}_2$  or  $\text{PhHgCBr}_3$ , gives a good yield of 2-chloro- or 2-bromo-3-phenylbenzo[b]thiophene.<sup>314</sup>

2,3-Diphenylbenzo[b]thiophene has been obtained from the reaction of 2-(methylthio)benzophenone with  $\text{PhCHCl}\cdot\text{CO}_2\text{H}$  (modified Krollpfeiffer reaction<sup>2</sup>)<sup>315</sup> and by heating  $\text{Ph}_2\text{CCl}\cdot\text{CHClPh}$  with sulfur at 240°C.<sup>316</sup> The most general synthesis of 2,3-diarylbenzo[b]thiophenes starts from 2-arylthio-1,2-diarylvinyl arenesulfonates **75** (Scheme 3).<sup>317-320</sup> These cyclize in the presence of  $\text{BF}_3$  to give, in cases where X = Me, MeO, Cl, or Br,<sup>318</sup>

<sup>310</sup> A. G. Anastassiou, J. C. Wetzel, and B. Chao, *J. Am. Chem. Soc.* **98**, 6405 (1976).

<sup>311</sup> M. G. Voronkov and V. Udre, *Khim. Seraorg. Soedin., Soderzh. Neflyakh Nefteprod.* **9**, 233 (1972) [*CA* **79**, 125981 (1973)].

<sup>312</sup> M. G. Voronkov and V. Udre, *Khim. Geterotsikl. Soedin.*, **43** (1968).

<sup>313</sup> T. J. Barton and R. G. Zika, *J. Org. Chem.* **35**, 1729 (1970).

<sup>314</sup> D. Seyferth, W. Tronich, R. S. Marmor, and W. E. Smith, *J. Org. Chem.* **37**, 1537 (1972).

<sup>315</sup> F. Sauter and A. Dzerovicz, *Monatsh. Chem.* **100**, 905 (1969).

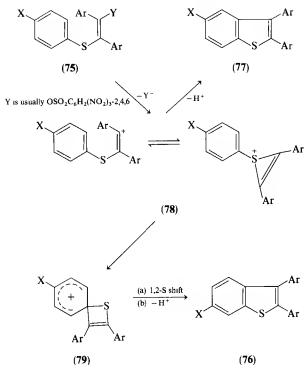
<sup>316</sup> M. G. Voronkov and V. Udre, USSR Patent 230,184 (1968) [*CA* **71**, 13013 (1969)].

<sup>317</sup> G. Capozzi, G. Melloni, and G. Modena, *J. Org. Chem.* **35**, 1217 (1970).

<sup>318</sup> G. Capozzi, G. Melloni, and G. Modena, *J. Chem. Soc. C*, 2621 (1970).

<sup>319</sup> G. Melloni and G. Modena, *J. C. S. Perkin I*, 218 (1972).

<sup>320</sup> G. Melloni and G. Modena, *J. C. S. Perkin I*, 1355 (1972).



SCHEME 3

the *rearranged* products **76**. If X is a strongly electron-withdrawing group, no rearrangement is observed and the 5-X-substituted benzo[*b*]thiophene **77** is formed.<sup>319</sup> If X = D, a 1:1 mixture of **76** and **77** is obtained.<sup>317</sup> If, in **75**, X is meta with respect to the sulfur atom, no rearrangement is observed for X = Me, MeO, Cl, or Br.<sup>318</sup> The reaction is believed to proceed via the vinylic carbonium ion **78**, either in its open-chain or cyclic form.<sup>321</sup> Ion **78** may then cyclize normally to **77**, or it may form the spiro intermediate **79**, which can rearrange to **76** via a 1,2-sulfur shift and loss of a proton. The sulfone of **75** behaves similarly, to give the appropriate 2,3-diarylbenzo[*b*]thiophene 1,1-dioxide.<sup>322</sup> The vinyl chloride **75** (Y = Cl) undergoes analogous cyclization with PPA-Ag<sub>2</sub>O.<sup>323</sup>

<sup>321</sup> G. Capozzi, G. Melloni, and G. Modena, *J. Chem. Soc. C*, 3018 (1971).

<sup>322</sup> G. Melloni and G. Modena, *Int. J. Sulfur Chem., Part A* **1**, 125 (1971).

<sup>323</sup> G. Capozzi, A. Di Bello, G. Melloni, and G. Modena, *Ric. Sci.* **39**, 267 (1969) [*CA* **72**, 100399 (1970)].

In a variant of the above method, the vinyl bromide **80** may be cyclized to the 2,3-diarylbenzo[b]thiophene either photolytically,<sup>324</sup> under basic conditions,<sup>325</sup> or in the presence of  $\text{Ag}^+ - \text{AcOH}$ .<sup>326</sup>

4- and 7-Phenylbenzo[b]thiophene have been prepared by photocyclization of 1-phenyl-4-(2- or 3-thienyl)buta-1,3-diene.<sup>327</sup> A mixture of 4- and 6-phenyl isomers is obtained by photoirradiation of a mixture of 4- and 6-iodobenzo[b]thiophenes in benzene.<sup>261</sup>

## 2. Preparation of Alkylbenzo[b]thiophenes

Thio-Claisen rearrangement of aryl 2-chloroprop-2-enyl sulfides ( $\text{ArSCH}_2\text{CCl}=\text{CH}_2$ ) affords a range of 5- and 7-substituted 2-methylbenzo[b]thiophenes in high yield.<sup>328</sup> Thiophenes containing a 2-( $\text{CHR} \cdot \text{CHMe} \cdot \text{CH}_2\text{CH}=\text{CH}_2$ ) side chain are cyclized by  $\text{AlCl}_3 - \text{BF}_3$  to give, after aromatization, 7-R-substituted 4,6-dimethylbenzo[b]thiophenes (> 80%).<sup>329</sup>

## 3. Reactions of Alkyl- and Arylbenzo[b]thiophenes

2-Alkyl- and 2-arylbenzo[b]thiophenes undergo electrophilic substitution in the 3-position.<sup>198,199,330</sup> 3-Methylbenzo[b]thiophene is nitrated in the 2- and 6-positions.<sup>331</sup> 5-Methylbenzo[b]thiophene undergoes 2,3-dibromination.<sup>332</sup> A reexamination of the nitration of 2,3-dimethylbenzo[b]thiophene has shown that, in addition to the previously observed products (Ref. 2, p.279) (viz., 6- $\text{NO}_2$ ; 3-Me, 2- $\text{CH}_2\text{NO}_2$ ; 3-Me, 2CHO), the 4-nitro isomer and the ring-opened product **57** are also obtained.<sup>251</sup> Tritium-exchange studies have confirmed that a 2- or 3-methyl group undergoes acid-catalyzed rearrangement to the corresponding exocyclic methylene tautomer, which may be the intermediate in side-chain substitution.<sup>333</sup>

<sup>324</sup> T. Suzuki, T. Sonoda, S. Kobayashi, and H. Taniguchi, *J. C. S., Chem. Commun.*, 180 (1976).

<sup>325</sup> T. Sonoda, M. Kawakami, T. Ikeda, S. Kobayashi, and H. Taniguchi, *J. C. S., Chem. Commun.*, 612 (1976).

<sup>326</sup> T. Sonoda, S. Kobayashi, and H. Taniguchi, *Chem. Lett.*, 389 (1976).

<sup>327</sup> C. C. Leznoff, W. Lilie, and C. Manning, *Can. J. Chem.*, **52**, 132 (1974).

<sup>328</sup> W. K. Anderson, E. J. La Voie, and J. C. Bottaro, *J. C. S. Perkin I*, 1 (1976).

<sup>329</sup> P. Canonne and J. Gourier, *C. R. Acad. Sci., Ser. C* **268**, 2319 (1969).

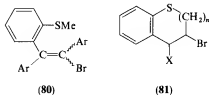
<sup>330</sup> R. Neidlein and M. H. Salzl, *Arch. Pharm. (Weinheim, Ger.)* **310**, 635 (1977).

<sup>331</sup> I. U. Numanov, G. Karimov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **14**, 41 (1971).

<sup>332</sup> R. P. Dickinson and B. Iddon, *J. Chem. Soc. C*, 2504 (1971).

<sup>333</sup> C. Eaborn and G. J. Wright, *J. Chem. Soc. B*, 2262 (1971).

The conversion,  $\text{ArMe} \rightarrow \text{ArCH}=\text{CHPh}$ , is effected by reaction of an appropriate methylbenzo[*b*]thiophene with the anil,  $\text{PhN}=\text{CHPh}$ , in the presence of  $\text{KOH-DMF}$ .<sup>334</sup> The methyl group must either be attached to the benzenoid ring of benzo[*b*]thiophene or, preferably, form part of a *p*-tolyl substituent. The resulting compounds are of importance as fluorescent whiteners.<sup>18</sup> Attention has again been drawn to the migration of methyl and phenyl groups in reactions involving  $\text{PPA}$  or  $\text{AlCl}_3$ , and to the possibility of debromination by the latter reagent.<sup>335,336</sup>



By treatment with  $\text{CHCl}_2\text{OMe}$  or  $\text{EtOCCl}_2 \cdot \text{CO}_2\text{Et}$  in the presence of  $\text{SnCl}_4$ , 2-allylbenzo[*b*]thiophene is converted into dibenzothiophene or its 1- $\text{CO}_2\text{Et}$  derivative, respectively (direct Bradsher reaction).<sup>337</sup> A substituted 2-allyl derivative (2- $\text{CH}_2\text{CMe}=\text{CH}_2$  or 2- $\text{CH}_2\text{CH}=\text{CHMe}$ ) behaves similarly.<sup>337,338</sup>

## D. HALOGEN DERIVATIVES

### 1. Preparation

Most halogenobenzo[*b*]thiophenes are still obtained by conventional methods (cf. Ref. 2). 4- and 6-Halogeno compounds remain relatively inaccessible since they are often obtained as a mixture from cyclization reactions. 4-Bromobenzo[*b*]thiophenes, however, have been made by deamination of the readily available 5-amino-4-bromo compounds.<sup>339,340</sup> Newer methods for preparing halogenobenzo[*b*]thiophenes via metallation reactions will be discussed in Section V.

<sup>334</sup> A. E. Siegrist and H. R. Meyer, *Helv. Chim. Acta* **52**, 1282 (1969).

<sup>335</sup> A. N. Kost, V. A. Budylin, E. D. Matveeva, and D. O. Sterligov, *J. Org. Chem. USSR (Engl. Transl.)* **6**, 1516 (1970).

<sup>336</sup> O. Dann, E. Hieke, H. Hahn, H.-H. Misserre, G. Lürding, and R. Rössler, *Justus Liebig's Ann. Chem.* **734**, 23 (1970).

<sup>337</sup> J. Ashby, M. Ayad, and O. Meth-Cohn, *J. C. S. Perkin I*, 1744 (1974).

<sup>338</sup> P. Cagniant, N. Bellinger, and D. Cagniant, *C. R. Acad. Sci., Ser. C* **277**, 383 (1973).

<sup>339</sup> N. B. Chapman, K. Clarke, B. A. Gore, and K. S. Sharma, *J. Chem. Soc. C*, 915 (1971).

<sup>340</sup> N. B. Chapman, K. Clarke, and S. N. Sawhney, *J. Chem. Soc. C*, 2747 (1968).

Prolonged low-temperature chlorination of benzo[b]thiophene in the presence of iodine gives an octachloro compound, in which chlorine has added across the 2,3-bond and substituted all hydrogen atoms.<sup>341</sup> Heating this to 240°C gives hexachlorobenzo[b]thiophene,<sup>341</sup> which can be reduced catalytically to 4,5,6,7-tetrachlorobenzo[b]thiophene.<sup>342</sup>

Heating the bromohydrins **81** (X = OH, *n* = 1 or 2) in dioxane gives 2-bromomethyl- or 2-(2-bromoethyl)benzo[b]thiophene, respectively, in excellent yield.<sup>343,344</sup>

## 2. Electrophilic Substitution Reactions

2-Halogenobenzo[b]thiophenes are brominated and formylated (Rieche method) in the 3-position.<sup>243,345</sup> Chlorination of 3-bromobenzo[b]thiophene in AcOH gives a mixture of 3-chloro-, 2,3-dichloro-, 2,3-dibromo-, 3-bromo-2-chloro- and/or 2-bromo-3-chloro-benzo[b]thiophenes.<sup>243</sup> Nitration of 2,3-dibromobenzo[b]thiophene gives the 4- and 6-nitro derivatives, together with smaller amounts of the 4- and 6-bromo derivatives.<sup>253</sup> Bromination of 2-bromo-3-methylbenzo[b]thiophene gives the 6-bromo product, but nitration gives a mixture of the 4- and 6-nitro isomers, together with ~40% of the ipso nitration product **56** (X = H).<sup>254</sup> 3-Bromo-2-methylbenzo[b]thiophene is nitrated in the 4- and 6-positions; 2-methyl-3-nitrobenzo[b]thiophene is also formed.<sup>251</sup> For 4- and 6-chlorobenzo[b]thiophene, while the product distribution depends on the type of substitution reaction, the former generally gives a mixture of the 2- and 3-substitution products, whereas the latter gives mainly the 3-isomer.<sup>244</sup> The 3-methyl derivatives of 4-, 6-, and 7-chlorobenzo[b]thiophene generally substitute almost entirely in the 3-position.<sup>244,250</sup>

## 3. Nucleophilic Substitution in Halogenobenzo[b]thiophenes

The reactions of 2- and 3-bromobenzo[b]thiophene with piperidine have been reexamined. The 2-isomer undergoes normal nucleophilic replacement, but the 3-isomer, which was previously (Ref. 2, p. 243) said to give a mixture of benzo[b]thiophene and 2-piperidinobenzo[b]thiophene, is now shown

<sup>341</sup> M. S. Raasch, *J. Org. Chem.* **45**, 2151 (1980).

<sup>342</sup> G. M. Brooke and R. King, *Tetrahedron* **30**, 857 (1974).

<sup>343</sup> H. Hofmann and G. Salbeck, *Angew. Chem., Int. Ed. Engl.* **8**, 456 (1969).

<sup>344</sup> A. Chatterjee and B. K. Sen, *J. C. S. Chem. Commun.*, 626 (1974).

<sup>345</sup> T. Q. Minh, P. Thibaut, L. Christiaens, and M. Renson, *Tetrahedron* **28**, 5393 (1972).

to give mainly the 3-piperidino compound, together with smaller amounts of the 2-isomer and up to 70% of starting material.<sup>216</sup>

With piperidine (and other secondary amines<sup>346</sup>), 2,3-dibromobenzo[*b*]thiophene gives mainly 2-piperidinobenzo[*b*]thiophene, i.e., nucleophilic substitution of the more reactive 2-substituent is accompanied by overall protodebromination of the 3-substituent.<sup>216</sup>

3-Bromobenzo[*b*]thiophene is recovered unchanged from  $\text{NaNH}_2$ -liquid  $\text{NH}_3$ , but the 2-bromo isomer gives a mixture of 3-bromobenzo[*b*]thiophene and benzo[*b*]thiophene; 2,3-dibromobenzo[*b*]thiophene gives 3-bromobenzo[*b*]thiophene. In no case can any amine be detected.<sup>214,215</sup> The above are probably intermolecular transhalogenation reactions involving benzo[*b*]thiophene carbanions, but it is believed that  $\text{NH}_2^-$  may also play a part in removing  $\text{Br}^+$ .

2-Iodo- and 3-bromobenzo[*b*]thiophene are each converted into the corresponding methoxy compound with  $\text{NaOMe}$ <sup>347</sup>; hexachlorobenzo[*b*]thiophene reacts selectively with thiophenoxide ion or hydride ion in the 2-position<sup>342</sup>; 2- and 3-bromo substituents are replaced by  $\text{ArO}^-$ ,  $\text{ArS}^-$ , or  $\text{ArNH}_2$  in DMF in the presence of copper salts.<sup>348,349</sup> The presence of an adjacent carbonyl function considerably enhances the lability of a 2- or 3-halogeno substituent.<sup>335,350,351</sup>

#### 4. Nucleophilic Substitution in Halogenobenzo[*b*]thiophene-1,1-Dioxides

Nucleophilic substitution in 2,3-dichlorobenzo[*b*]thiophene 1,1-dioxides takes place preferentially in the 3-position.<sup>352</sup> 2-Bromobenzo[*b*]thiophene 1,1-dioxide is converted into the 3-bromo isomer by  $\text{KNH}_2\text{-NH}_3$ <sup>215</sup>; it is well established that a 2-bromine atom is replaced by a nucleophile with rearrangement to give the 3-substituted product.<sup>1</sup> A 3-chloro substituent, activated by an adjacent ester or ketone function, is very readily replaced, and cyclization can often take place to form an additional heterocyclic ring.<sup>181,213,353</sup>

<sup>346</sup> K. E. Chippendale, B. Iddon, H. Suschitzky, and D. S. Taylor, *J. C. S. Perkin I*, 1168 (1974).

<sup>347</sup> P. Netchitailo, B. Decroix, J. Morel, and P. Pastour, *J. Heterocycl. Chem.* **15**, 337 (1978).

<sup>348</sup> J. Ashby, M. Ayad, and O. Meth-Cohn, *J. C. S. Perkin I*, 1104 (1973).

<sup>349</sup> E. F. Elslager, N. F. Haley, J. R. McLean, D. Potoczak, and H. Veloso, *J. Med. Chem.* **15**, 61 (1972).

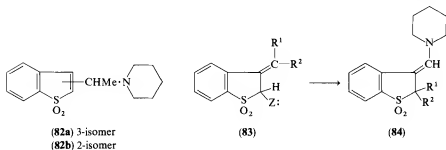
<sup>350</sup> R. Neidlein and H. Heid, *Synthesis*, 65 (1977).

<sup>351</sup> A. Ricci, D. Balucani, and M. Bettelli, *Gazz. Chim. Ital.* **101**, 774 (1971).

<sup>352</sup> E. g. V. Udre and E. Lukevics, *Khim. Geterotsikl. Soedin.*, 56 (1977).

<sup>353</sup> W. Ried and W. Ochs, *Justus Liebigs Ann. Chem.*, 1248 (1974).

Bordwell *et al.*<sup>354-358</sup> have made an extensive study of the rearrangement reactions brought about by nucleophilic attack on a range of substituted halogenobenzo[*b*]thiophene-1,1-dioxides. 3-Chloromethyl- and 2-bromo-3-methylbenzo[*b*]thiophene-1,1-dioxide each give the same product with piperidine, the structure of which (Ref. 2, p. 358) has now been amended to **84** ( $R^1 = R^2 = H$ ). With piperidine, 2-bromo-3-ethyl- and 2-ethyl-3-bromobenzo[*b*]thiophene-1,1-dioxides give amines **82a** and **82b**, respectively.<sup>354</sup>



1,1-Dioxides containing a 3- $\text{CCl}\cdot\text{R}^1\text{R}^2$  substituent react with piperidine to give **84**. An initial addition-elimination reaction ( $\text{S}_{\text{N}}2'$ ) gives **83** ( $\text{Z} = \text{piperidino}$ ), which then undergoes ring opening-ring closing isomerization to **84**. The lone pair of electrons on the substituent  $\text{Z}$  in **83** provides the driving force for the latter reaction; if  $\text{Z}$  lacks a lone pair (e.g.,  $\text{Z} = \text{CN}, \text{N}_3$ ), reaction stops at **83**.<sup>358</sup>

## E. NITRO AND AZIDO COMPOUNDS

### 1. Preparation

3-Nitrobenzo[*b*]thiophene is obtained pure, albeit in low yield, from the nitration of benzo[*b*]thiophene-3-carboxylic acid.<sup>234</sup> It is said to be formed when benzo[*b*]thiophene reacts with  $\text{NO}_2$  and air in acetic acid.<sup>359</sup> 4-, 6-, and 7-Nitrobenzo[*b*]thiophene are each obtained pure by decarboxylation of the corresponding 3-carboxylic acid.<sup>234</sup>

<sup>354</sup> F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.* **33**, 3226 (1968).

<sup>355</sup> F. G. Bordwell, R. W. Hemwall, and D. A. Schexnayder, *J. Org. Chem.* **33**, 3233 (1968).

<sup>356</sup> F. G. Bordwell and D. A. Schexnayder, *J. Org. Chem.* **33**, 3236 (1968).

<sup>357</sup> F. G. Bordwell and D. A. Schexnayder, *J. Org. Chem.* **33**, 3240 (1968).

<sup>358</sup> F. G. Bordwell and T. G. Mecca, *J. Am. Chem. Soc.* **94**, 5825 (1972).

<sup>359</sup> N. A. Kazbula, S. M. Maksimov, M. F. Pankratova, and N. P. Anashkina, USSR Patent 215,923 (1968) [*CA* **69**, 43784 (1968)].



Azidobenzo[b]thiophenes are prepared via the corresponding diazonium salts, by treatment of a Grignard reagent with toluene-*p*-sulfonyl azide and sodium pyrophosphate<sup>360</sup> or from organolithium derivatives (Section V).

## 2. Reactions of Nitrobenzo[b]thiophenes

The order of reactivity of the various positions in 3-nitrobenzo[b]thiophene toward nitration is  $6 > 5 > 4 > 7$ ; no 2-substitution is observed.<sup>234</sup> 3-Methyl-2-nitrobenzo[b]thiophene is nitrated in the 5-position.<sup>361</sup>

Treatment of 2-methyl-3-nitrobenzo[b]thiophene with *p*-nitroso-*N,N*-dimethylaniline gives, not the expected anil,  $2\text{-CH=NO}\cdot\text{C}_6\text{H}_4\cdot\text{NMe}_2\text{-}p$ , but mainly the nitrone,  $2\text{-CH=NO}\cdot\text{C}_6\text{H}_4\cdot\text{NMe}_2\text{-}p$ .<sup>362</sup> 5-Nitrobenzo[b]thiophene reacts with a THF solution of a Grignard reagent, RMgBr, in two ways: (1) in the presence of CuI, to give the 4-*R*-substituted 5-amino compound,<sup>363</sup> and (2) with BF<sub>3</sub>, to give the 4-*R*-substituted 5-nitroso compound.<sup>364</sup> The stabilities of the Meisenheimer complexes formed from 2-methoxy-3-nitro- or 3-methoxy-2-nitrobenzo[b]thiophene and methoxide ion have been investigated.<sup>365</sup>

## 3. Reactions Involving Nitrenes

Work in this area is attributable almost entirely to the Salford group, who have photolyzed or pyrolyzed azides and treated nitro compounds with triethyl phosphite (TEP). Although there is doubt as to whether the latter reaction proceeds via nitrene intermediates, it is convenient to include it in this section.

Attempts to obtain ring-expanded products by photolysis of azides in the presence of diethylamine were successful only for the 6-azido compound (Section III.C).<sup>193</sup> 4-Azidobenzo[b]thiophene gave, *inter alia*, 4-aminobenzo[b]thiophene and 4,4'-azobenzo[b]thiophene, probably via triplet nitrene.<sup>366</sup> The 5-azido isomer gave 4-amino-5-diethylaminobenzo[b]thiophene, probably via an azirine intermediate, derived from singlet nitrene. Thermolysis of 4-azidobenzo[b]thiophene in PPA-AcOH gave 4-acetamido-

<sup>360</sup> B. Iddon, H. Suschitzky, D. S. Taylor, and M. W. Pickering, *J. C. S. Perkin I*, 575 (1974).

<sup>361</sup> I. U. Numanov, I. M. Nasyrov, and G. Karimov, *Dokl. Akad. Nauk Tadzh. SSR* **14**, 38 (1971).

<sup>362</sup> V. M. Colburn, B. Iddon, and H. Suschitzky, *J. C. S. Perkin I*, 2436 (1977).

<sup>363</sup> G. Bartoli, A. Medici, G. Rosini, and D. Tavernari, *Synthesis*, 436 (1978).

<sup>364</sup> G. Bartoli, R. Leardini, A. Medici, and G. Rosini, *J. C. S. Perkin I*, 692 (1978).

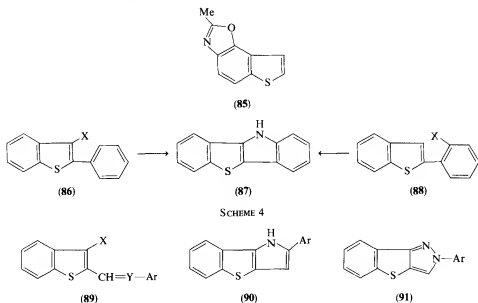
<sup>365</sup> F. De Santis and F. Stegel, *Gazz. Chim. Ital.* **103**, 649 (1973).

<sup>366</sup> B. Iddon, H. Suschitzky, and D. S. Taylor, *J. C. S. Perkin I*, 579 (1974).

7-acetoxybenzo[*b*]thiophene by means of a Bamberger-like rearrangement.<sup>360</sup> Similar treatment of the 5- and 6-azides yielded angular fused oxazole derivatives, by cyclization into the 4- and 7-positions (e.g., **85** from the former), but the corresponding 1,1-dioxides cyclized into the 6- and 5-positions, respectively, to give linear oxazole derivatives.<sup>193,360</sup> 3-Azido-benzo[*b*]thiophene did not give any cyclized products.<sup>367</sup>

Derivatives of [1]benzothieno[3,2-*b*]indole (**87**) are readily formed by heating the nitro compounds **86** or **88** ( $X = \text{NO}_2$ ) with TEP or by thermolysis of the corresponding azides ( $X = \text{N}_3$ ) (Scheme 4).<sup>368</sup> Similar treatment of the alkenes **89** ( $X = \text{NO}_2$ ,  $Y = \text{CH}$ ) gives the [1]benzothieno[3,2-*b*]pyrroles (**90**). The [2,3-*b*]-isomers of **90** are obtained analogously.<sup>369</sup> The [1]benzothieno[3,2-*c*]pyrazoles (**91**) are obtained by use of the anils **89** ( $X = \text{NO}_2$  or  $\text{N}_3$ ,  $Y = \text{N}$ ), but the isomeric [2,3-*c*]pyrazoles are accompanied by other products when they are prepared from the appropriate 2- $\text{NO}_2$  or 2- $\text{N}_3$ , 3- $\text{CH}=\text{NAr}$  benzo[*b*]thiophene derivative.<sup>370</sup>

Thermolysis of the sulfide **92** gives three main products, formed via the spiro intermediate **93**.<sup>371</sup>



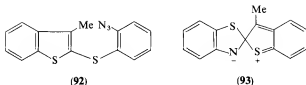
<sup>367</sup> P. Spagnolo and P. Zanirato, *J. Org. Chem.* **43**, 3539 (1978).

<sup>368</sup> K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. C. S. Perkin I*, 2023 (1972).

<sup>369</sup> K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. C. S. Perkin I*, 125 (1973).

<sup>370</sup> K. E. Chippendale, B. Iddon, and H. Suschitzky, *J. C. S. Perkin I*, 129 (1973).

<sup>371</sup> D. G. Hawkins, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 3207 (1979).



## F. AMINES

### 1. 2-Aminobenzo[b]thiophenes

a. *Preparation.* 2-*N,N*-Dialkylaminobenzo[b]thiophenes have been obtained by three general methods: (a) by treatment of 2,3-dibromobenzo[b]thiophene with a secondary amine,<sup>346</sup> (b) by addition of a cyclic secondary amine to benzo[b]thiophene and dehydrogenation of the resulting 2,3-dihydro compound,<sup>134</sup> and (c) by heating thiooxindole with a secondary amine in HMPA.<sup>267</sup>

b. *Reactions.* 2-*N,N*-Dialkylaminobenzo[b]thiophenes possess enamine character (NMR spectra), and react with acetyl chloride in benzene, to give the 3-acetyl derivative.<sup>346</sup>

2-Aminobenzo[b]thiophene gives the benzothienopyridone **94** with ethyl acetoacetate.<sup>372</sup> 2-Acetamidobenzo[b]thiophene reacts with  $P_2S_5$ , then the resulting thioamide is cyclized by  $K_3FeCN_6$ , to give the benzothienothiazole derivative **95** ( $X = S$ ,  $Y = Me$ ).<sup>373</sup> The analogous compound **95** ( $X = S$ ,  $Y = NH_2$ ) is prepared by oxidative thiocyanation of 2-aminobenzo[b]thiophene and cyclization of the resulting 3-thiocyanato derivative.<sup>374</sup> The oxygen analog **95** ( $X = O$ ,  $Y = Me$ ) is obtained by heating 2-acetamido-3-hydroxybenzo[b]thiophene.<sup>278</sup>

2-Acylamido-4,5,6,7-tetrahydrobenzo[b]thiophenes undergo the Mannich reaction,<sup>375</sup> Vilsmeier-Haack formylation,<sup>376</sup> diazo coupling,<sup>377</sup> and thiocyanation<sup>378</sup> to give the 3- $CH_2NHR$ , 3-CHO, 3- $N=NAr$ , and 3-SCN derivatives, respectively; the last can be cyclized to **95** ( $X = S$ ,  $Y = NHAc$ ).<sup>378</sup>

<sup>372</sup> P. I. Abramenko, *Zh. Vses. Khim. O-va.* **17**, 478 (1972) [*CA* **77**, 152020 (1972)].

<sup>373</sup> P. I. Abramenko and V. G. Zhiryakov, *Khim. Geterotsikl. Soedin.*, 1495 (1977).

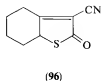
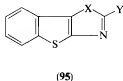
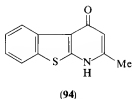
<sup>374</sup> K. Gewald, M. Hentschel, and R. Heikel, *J. Prakt. Chem.* **315**, 539 (1973).

<sup>375</sup> V. I. Shvedov, I. A. Kharizomenova, N. V. Medvedeva, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 918 (1975).

<sup>376</sup> V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 58 (1974).

<sup>377</sup> V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1624 (1973).

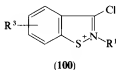
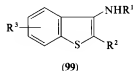
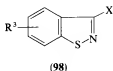
<sup>378</sup> V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1204 (1974).



3-Acyl- (3-COR) and 3-ethoxycarbonyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thiophenes undergo a novel base-catalyzed ring-opening/ring-closure reaction; the former gives the corresponding 2-R-substituted 3-cyano-4,5,6,7-tetrahydro compound, whereas the latter gives **96**.<sup>379</sup> 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile undergoes ring fission with PhMgBr to give nitrile **97**.<sup>380</sup>

## 2. 3-Aminobenzo[b]thiophenes

a. *Preparation.* 3-Aminobenzo[b]thiophenes **99** containing an electron-withdrawing 2-substituent may be obtained from 1,2-benzisothiazole derivatives **98**. 3-Chloro-1,2-benzisothiazole (**98** X = Cl, R<sup>3</sup> = H) reacts with acetylacetone, diethyl malonate (or ethyl acetoacetate), or cyanoacetamide, to give the 2-acetyl, 2-ethoxycarbonyl, and 2-carboxamido derivatives **99** (R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = Ac, CO<sub>2</sub>Et, or CONH<sub>2</sub>), respectively.<sup>381,382</sup> The 3-chloro-1,2-benzisothiazolium salts **100** react with methyl ketones, R'COMe, or with "activated methyl" compounds, R<sup>2</sup>Me (e.g., 4-methylpyridine), to give the aminobenzo[b]thiophenes **99** (R<sup>2</sup> = COR' in the former case).<sup>383,384</sup>



<sup>379</sup> O. Meth-Cohn and B. Narine, *J. Chem. Res. (S)*, 294; (*M*), 3262 (1977).

<sup>380</sup> R. Heckendorn and A. R. Gagneux, *Tetrahedron Lett.*, 2279 (1973).

<sup>381</sup> D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. C*, 3903 (1971).

<sup>382</sup> T. Vitali, F. Mossini, R. M. Mingiardi, E. Gaetani, and V. Plazzi, *Ateneo Parmense, Sez. 2* **7**, 71 (1971) [*CA* **77**, 15390 (1972)].

<sup>383</sup> H. Böshagen and W. Geiger, *Justus Liebigs Ann. Chem.*, **764**, 58 (1972).

<sup>384</sup> H. Böshagen and W. Geiger, *Synthesis*, 442 (1979).

It was concluded that the reactions involving the 3-chloro compound **98** ( $X = Cl$ ,  $R^3 = H$ ) proceed via the anion of *o*-mercaptobenzonitrile **101** ( $R^3 = H$ ). Indeed, authentic **101** ( $R^3 = H$ ) reacted in dilute alkali with the halogeno compounds,  $R^2CH_2Cl$  ( $R^2 = Ac$ ,  $Bz$ ,  $CN$ , or  $NO_2$ ), to give the corresponding aminobenzo[*b*]thiophenes **99** ( $R^1 = R^3 = H$ ).<sup>381</sup>

New methods for preparing *o*-mercaptobenzonitriles **101** have allowed this reaction to be extended to ring-substituted 3-aminobenzo[*b*]thiophenes **99** ( $R^1 = H$ ). In the first, substituted *o*-chlorobenzaldehydes react directly with sulfur and ammonia to give a 1,2-benzisothiazole **98** ( $X = H$ ), which undergoes base-catalyzed ring opening to **101**.<sup>385</sup> In Beck's elegant method, an *o*-nitrobenzonitrile is treated with  $Na_2S-R^2CH_2Cl$  or with  $R^2CH_2SH$  in DMF in the presence of base; the nitro group is expelled, and the amines **99** (e.g.,  $R^1 = H$ ,  $R^2 = Ph$ ,  $CO_2Me$ ,  $COR'$ , or  $CN$ ) are formed directly.<sup>386-388</sup>

3-Methyl-1,2-benzisothiazoles (**98**,  $X = Me$ ) are rearranged by  $POCl_3$ -DMF, to give the formamidines **99** ( $HR^1 = :CHNMe_2$ ,  $R^2 = H$  or  $CHO$ ) and/or the formamido compounds **99** ( $R^1 = CHO$ ,  $R^2 = H$ ).<sup>389,390</sup>

3-Pyrrolidinobenzo[*b*]thiophene and related compounds are conveniently obtained by treating thioindoxyl with the appropriate cyclic secondary amine in the presence of toluene-*p*-sulfonic acid.<sup>391,392</sup>

3-Acetamidobenzo[*b*]thiophene is obtained by reductive acetylation of the 3-nitro compound with  $Fe-AcOH-Ac_2O$ .<sup>393</sup> Unstable 3-aminobenzo[*b*]thiophene is best prepared *in situ* by decarboxylation of the corresponding 2-carboxylic acid.<sup>389</sup>

b. *Reactions.* 3-Pyrrolidinobenzo[*b*]thiophene is best regarded as an enamine (spectra).<sup>392</sup> As such, it undergoes cycloaddition reactions,<sup>170</sup> is alkylated (by allyl or benzyl halides) and acylated in the 2-position,<sup>394</sup> and undergoes Michael-type addition to  $\alpha,\beta$ -unsaturated ketones.<sup>395</sup>

2-Substituted 3-aminobenzo[*b*]thiophenes provide a useful source of the following tricyclic systems **102** and **103**, which have been prepared by the reactions indicated in parentheses: pyrroles **102** ( $X = NH$ ,  $Y = C \cdot CO_2H$ ,

<sup>385</sup> J. Markert and H. Hagen, *Justus, Liebigs Ann. Chem.*, 768 (1980).

<sup>386</sup> J. R. Beck and J. A. Yahner, *J. Org. Chem.* **39**, 3440 (1974).

<sup>387</sup> J. R. Beck, *J. Org. Chem.* **37**, 3224 (1972).

<sup>388</sup> J. R. Beck, *J. Heterocycl. Chem.* **15**, 513 (1978).

<sup>389</sup> D. E. L. Carrington, K. Clarke, C. G. Hughes, and R. M. Scrowston, *J. C. S. Perkin I*, 3006 (1972).

<sup>390</sup> K. Clarke, B. Gleadhill, and R. M. Scrowston, *J. Chem. Res. (S)*, 197; (*M*), 2845 (1980).

<sup>391</sup> D. N. Reinhoudt, W. P. Trompenaars, and J. Gevers, *Synthesis*, 368 (1978).

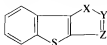
<sup>392</sup> J. Weber and P. Faller, *Bull. Soc. Chim. Fr.*, 783 (1975).

<sup>393</sup> L. H. Klemm and W. Hsin, *J. Heterocycl. Chem.* **12**, 1183 (1975).

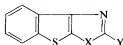
<sup>394</sup> J. Weber and P. Faller, *C. R. Acad. Sci., Ser. C* **281**, 389 (1975).

<sup>395</sup> M. Schaefer, J. Weber, and P. Faller, *Synthesis*, 122 (1979).

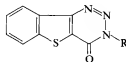
Z = CH) (reduction of 3-NO<sub>2</sub>, 2-CH<sub>2</sub>COCO<sub>2</sub>H)<sup>396</sup>; imidazoles **103** (X = NH, Y = Me) (heating 2,3-diNHAc)<sup>397</sup>; isothiazoles **102** (X = S, Y = N, Z = CR) (heating in PPA the cyclic product formed from 2-CHO, 3-SCN and NH<sub>2</sub>OH)<sup>398</sup>; imidazole N-oxides **102** (X = NH, Y = CPh, Z = N<sup>+</sup>—O<sup>-</sup>) (base-catalyzed cyclization of 2-NO<sub>2</sub>, 3-NHCH<sub>2</sub>Ph)<sup>399</sup>; oxazoles **103** (X = O, Y = Me) (heating 2-OH, 3-NHAc)<sup>278</sup>; thiazoles **103** (X = S, Y = SH) (Na<sub>2</sub>S-CS<sub>2</sub> on the cyclic product from 3-NH<sub>2</sub>·HCl and S<sub>2</sub>Cl<sub>2</sub>).<sup>400</sup> The benzothienotriazines **104** (R = H or Me) are obtained by diazotization of the 2-CONHR derivative of 3-aminobenzo[b]thiophene.<sup>401-403</sup>



(102)



(103)



(104)

### 3. 4-, 5-, 6-, and 7-Aminobenzo[b]thiophenes

Remarkably little has been published recently on these amines. 4-Aminobenzo[b]thiophene may be prepared from the 4-hydroxy compound, either by the Bucherer reaction,<sup>404</sup> or by forming the 4-OCMe<sub>2</sub>·CONH<sub>2</sub> compound, which then undergoes Smiles rearrangement with NaH-HMPA. Hydrolysis of the product (4-NHCOCMe<sub>2</sub>·OH) gives 4-aminobenzo[b]thiophene in high overall yield.<sup>405</sup>

7-Aminobenzo[b]thiophene is obtained by heating the corresponding 7-chloro compound with ammonia in the presence of CuCl.<sup>250</sup>

4-Aminobenzo[b]thiophene does not undergo the Bucherer reaction, but hydrolysis with 15% H<sub>3</sub>PO<sub>4</sub> under carefully controlled conditions gives the 4-hydroxy compound (~90%).<sup>404</sup> 4,5-Diaminobenzo[b]thiophene derivatives are useful precursors for a range of tricyclic heteroaromatic

<sup>396</sup> O. P. Shkurko and V. P. Mamaev, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 112 (1967) [*CA* **69**, 27290 (1968)].

<sup>397</sup> P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 1473 (1970).

<sup>398</sup> K. Clarke, W. R. Fox, and R. M. Scrowston, *J. Chem. Res. (S)*, 33; (*M*), 833 (1980).

<sup>399</sup> P. N. Preston and S. K. Sood, *J. C. S. Perkin I*, 80 (1976).

<sup>400</sup> N. I. Astrakhantseva, V. G. Zhiryakov, and P. I. Abramenko, *Khim. Geterotsikl. Soedin.*, 1355 (1976).

<sup>401</sup> J. R. Beck and J. A. Yahner, *J. Org. Chem.*, **38**, 2450 (1973).

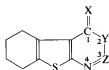
<sup>402</sup> J. R. Beck and J. A. Yahner, *J. Org. Chem.*, **41**, 1733 (1976).

<sup>403</sup> S. W. Schneller and F. W. Clough, *Heterocycles*, **3**, 135 (1975).

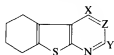
<sup>404</sup> D. E. Boswell, J. A. Brennan, and P. S. Landis, *Tetrahedron Lett.*, 5265 (1970).

<sup>405</sup> R. Bayles, M. C. Johnson, R. F. Maisey, and R. W. Turner, *Synthesis*, 33 (1977).

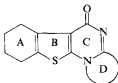
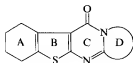
TABLE II  
TRI- AND TETRACYCLIC SYSTEMS BASED ON 3-SUBSTITUTED  
2-AMINO-4,5,6,7-TETRAHYDROBENZO[b]THIOPHENES (106)<sup>a</sup>



X	Y	Z	Ref.
O	NH	C·Ar	408–412
S	NH	C·Ar	410
O	NH	C·R	409, 412–414
O	NAr	C·Ar	415
O	NAr	C·R	414, 416, 417
O	NH	C·CH <sub>2</sub> N<	418
O	N·NH <sub>2</sub>	C·CH <sub>2</sub> N<	419
O	NR	C·SH	420–422
O	NH	C·SH	422, 423
O	NAr	C·SH	424, 425
O	NAr	C·SR	426
O	NH	C·OH	427
O	NR	C·OH	428
O	NAr	C·OH	416
O	NR	N	429
S	S	C·R	430
O	NH	C·SeH	431
O	NH or O	C·CO <sub>2</sub> R	432
NH	N·NH <sub>2</sub>	CH	433
O	CH·NO <sub>2</sub>	C·NHPh	434
O	CH·CO <sub>2</sub> Et	CH	435
O	NH	(4-NH)·B·Ph	436



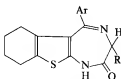
NH <sub>2</sub>	H	N	414
NH <sub>2</sub>	Me	C·CO <sub>2</sub> Me	437
Ph	R	C·R'	438
Ph	SMe	C·NO <sub>2</sub>	439
Ph	OH	N	440
NH <sub>2</sub>	NH <sub>2</sub>	N	441, 442



<sup>a</sup> The compounds described do not necessarily exist in the tautomeric form indicated by the formulas.

TABLE II (Continued)

Ring D <sup>b</sup>	Ref.	Ring D <sup>b</sup>	Ref.
CH:CH·CH:CH	415	(CH <sub>2</sub> ) <sub>3</sub>	447
CH <sub>2</sub> ·CHMe·S	443	CMe:CH·S	448
(CH <sub>2</sub> ) <sub>n</sub>	444		
SO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> (1,2)	445		
CH <sub>2</sub> ·CH(CH <sub>2</sub> Br)·S	446		



Ref. 449-451

<sup>b</sup> The first atom of the substituent shown is joined to the C/D bridgehead nitrogen atom.

systems.<sup>366,406</sup> *o*-Chlorobenzaldehyde forms an anil with 4-aminobenzo[b]thiophene, which is cyclized by KNH<sub>2</sub>-NH<sub>3</sub>, via an aryne intermediate, to thieno[2,3-*c*]phenanthridine (**105**).<sup>407</sup> 6-Acetamidobenzo[b]thiophene is nitrated in the 2- and 7-positions, brominated (in AcOH) in the 2-position, and acylated (Friedel-Crafts) in the 2- and 3-positions.<sup>244</sup>

#### 4. Polycyclic Systems from 3-Substituted 2-Amino-4,5,6,7-tetrahydrobenzo[b]thiophenes

The 3-substituted 2-aminobenzo[b]thiophenes **106** (X = CN, CO<sub>2</sub>R, CONH<sub>2</sub>, COAr) are readily available by means of Karl Gewald's elegant synthesis (Ref. 2, p. 209), and medicinal chemists have been quick to realize their value as a source of polycyclic derivatives of potential biological importance. A representative sample of such compounds is given in Table II.<sup>408-451</sup>

<sup>406</sup> N. B. Chapman, K. Clarke, and K. S. Sharma, *J. Chem. Soc. C*, 919 (1971).

<sup>407</sup> S. V. Kessar, P. K. Khullar, and P. Jit, *Indian J. Chem.* **11**, 1191 (1973).

<sup>408</sup> F. Sauter, P. Stanetty, H. Potuzak, and M. Baradar, *Monatsh. Chem.* **107**, 669 (1976).

<sup>409</sup> H. K. Gakhar, P. M. Singh, A. Madan, and N. Kumar, *Indian J. Chem., Sect. B* **16**, 940 (1978).

<sup>410</sup> M. S. Manhas, S. G. Amin, and B. Dayal, *J. Heterocycl. Chem.* **13**, 633 (1976).

<sup>411</sup> M. S. Manhas, S. G. Amin, S. D. Sharma, B. Dayal, and A. K. Bose, *J. Heterocycl. Chem.* **16**, 371 (1979).

<sup>412</sup> F. Sauter, *Monatsh. Chem.* **99**, 1507 (1968).

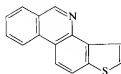
<sup>413</sup> M. S. Manhas, S. G. Amin, and V. V. Rao, *Synthesis*, 309 (1977).

<sup>414</sup> M. B. Devani, C. J. Shishoo, U. S. Pathak, S. H. Parikh, A. V. Radhakrishnan, and A. C. Padhya, *Indian J. Chem., Sect. B* **14**, 357 (1976).

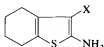


Footnotes (continued from pg. 225)

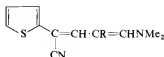
- <sup>415</sup> M. S. Manhas and S. G. Amin, *J. Heterocycl. Chem.* **13**, 903 (1976).  
<sup>416</sup> F. Sauter, G. Reich, and P. Stanetty, *Arch. Pharm. (Weinheim, Ger.)* **309**, 908 (1976).  
<sup>417</sup> M. S. Manhas and S. G. Amin, *J. Heterocycl. Chem.* **14**, 161 (1977).  
<sup>418</sup> F. Sauter, *Monatsh. Chem.* **99**, 2100 (1968).  
<sup>419</sup> F. Sauter, P. Stanetty, and H. Potuzak, *Arch. Pharm. (Weinheim, Ger.)* **309**, 914 (1976).  
<sup>420</sup> I. V. Smolanka and A. A. Dobosh, *Ukr. Khim. Zh. (Russ. Ed.)* **39**, 402 (1973) [*CA* **79**, 32001 (1973)].  
<sup>421</sup> M. B. Devani, C. J. Shishoo, U. S. Pathak, S. H. Parikh, G. F. Shah, and A. C. Padhya, *J. Pharm. Sci.* **65**, 660 (1976).  
<sup>422</sup> F. Sauter and W. Deinhammer, *Monatsh. Chem.* **104**, 1593 (1973).  
<sup>423</sup> A. A. Dobosh, S. M. Khripak, and I. V. Smolanka, *Khim. Geterotsikl. Soedin.*, 486 (1974).  
<sup>424</sup> M. B. Devani, C. J. Shishoo, U. S. Pathak, B. G. Sharma, S. V. Gokhale, and A. C. Padhya, *Indian J. Chem., Sect. B* **15**, 575 (1977).  
<sup>425</sup> S. M. Khripak, A. A. Dobosh, and I. V. Smolanka, *Khim. Geterotsikl. Soedin.*, 567 (1973).  
<sup>426</sup> I. V. Smolanka, S. M. Khripak, N. P. Frolova, and A. A. Dobosh, *Ukr. Khim. Zh. (Russ. Ed.)* **45**, 871 (1979) [*CA* **92**, 6490 (1980)].  
<sup>427</sup> F. Sauter, *Monatsh. Chem.* **101**, 535 (1970).  
<sup>428</sup> L. Capuano, M. Welter, and R. Zander, *Chem. Ber.* **102**, 3698 (1969).  
<sup>429</sup> F. Sauter and W. Deinhammer, *Monatsh. Chem.* **104**, 1586 (1973).  
<sup>430</sup> S. Leistner and G. Wagner, *Z. Chem.* **17**, 95 (1977).  
<sup>431</sup> I. V. Smolanka, S. M. Khripak, A. A. Zeikan, and A. A. Dobosh, *Khim. Geterotsikl. Soedin.*, 753 (1977).  
<sup>432</sup> D. L. Temple, J. P. Yevich, R. R. Covington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey, and M. J. Bartek, *J. Med. Chem.* **22**, 505 (1979).  
<sup>433</sup> F. Sauter and P. Stanetty, *Monatsh. Chem.* **106**, 1111 (1975).  
<sup>434</sup> H. Schäfer, K. Gewald, and M. Seifert, *J. Prakt. Chem.* **318**, 39 (1976).  
<sup>435</sup> Y. Kuwada, K. Meguro, Y. Sato, and T. Fugono, *Ger. Offen.* 2,435,025 (1975) [*CA* **82**, 156252 (1975)].  
<sup>436</sup> V. P. Arya, *Indian J. Chem., Sect. B* **15**, 267 (1977).  
<sup>437</sup> I. Lalezari, *J. Heterocycl. Chem.* **16**, 603 (1979).  
<sup>438</sup> H. Schäfer, K. Gewald, and H. Hartmann, *J. Prakt. Chem.* **316**, 169 (1974).  
<sup>439</sup> H. Schäfer, B. Bartho, and K. Gewald, *Z. Chem.* **13**, 294 (1973).  
<sup>440</sup> T. Hiroyashi, H. Sato, S. Inaba, and H. Yamamoto, *Ger. Offen.* 2,323,149 (1973) [*CA* **80**, 70825 (1974)].  
<sup>441</sup> A. Rosowsky, M. Chaykovsky, K. K. N. Chen, M. Lin, and E. J. Modest, *J. Med. Chem.* **16**, 185 (1973).  
<sup>442</sup> E. F. Elslager, P. Jacob, and L. M. Werbel, *J. Heterocycl. Chem.* **9**, 775 (1972).  
<sup>443</sup> H. K. Gakhar, A. Madan, A. Khanna, and N. Kumar, *J. Indian Chem. Soc.* **55**, 705 (1978).  
<sup>444</sup> V. I. Shvedov, I. A. Kharizomenova, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 765 (1975).  
<sup>445</sup> F. Sauter and W. Deinhammer, *Monatsh. Chem.* **105**, 1249 (1974).  
<sup>446</sup> A. A. Dobosh, I. V. Smolanka, and S. M. Khripak, *Khim. Geterotsikl. Soedin.*, 134 (1974).  
<sup>447</sup> M. S. Manhas, V. V. Rao, and S. G. Amin, *J. Heterocycl. Chem.* **13**, 821 (1976).  
<sup>448</sup> F. Sauter and W. Deinhammer, *Monatsh. Chem.* **105**, 452 (1974).  
<sup>449</sup> F. J. Tinney, J. P. Sanchez, and J. A. Nogas, *J. Med. Chem.* **17**, 624 (1974).  
<sup>450</sup> M. Nakanishi, T. Tahara, K. Araki, M. Shiroki, T. Tsumagari, and Y. Takigawa, *J. Med. Chem.* **16**, 214 (1973).  
<sup>451</sup> M. Murakami, N. Inukai, and K. Nakano, Japanese Patent 73/12,760 (1973) [*CA* **79**, 42567 (1973)].



(105)



(106)



(107)

## G. NITRILES

In a novel synthesis of 5-*R*-substituted benzo[*b*]thiophene-7-carbonitriles, (2-thienyl)acetonitrile reacts with the trimethinium perchlorate,  $\text{Me}_2\text{N}^+=\text{CHCR}=\text{CHNMe}_2 \text{ ClO}_4^-$ , in the presence of NaOMe. The resulting compounds **107** cyclize thermally with loss of dimethylamine to give the appropriate 7-cyano derivative.<sup>452</sup>

## H. DERIVATIVES WITH NITROGEN IN A SIDE CHAIN

## 1. Amines

Interest in the benzo[*b*]thiophene isosteres of biologically active indoles continues unabated, and many analogs with a  $-\text{CH}_2\text{CH}_2\text{NH}_2$  or  $-\text{CH}_2\text{CH}_2\text{NR}_2$  side chain, particularly in the 3-position, have been prepared. The general methods used are summarized in Scheme 5,<sup>453-463</sup> and can, of course, be adapted for preparing longer amino side chains. By these

<sup>452</sup> C. Jutz, R. M. Wagner, and H.-G. Löbering, *Angew. Chem., Int. Ed. Engl.* **13**, 737 (1974).

<sup>453</sup> F. Sauter and P. Stütz, *Monatsh. Chem.* **99**, 2095 (1968).

<sup>454</sup> N. B. Chapman, K. Clarke, A. J. Humphries, and S. U.-D. Saraf, *J. Chem. Soc. C*, 1612 (1969).

<sup>455</sup> R. Neidlein and C. Gehringer, *Arch. Pharm. (Weinheim, Ger.)* **307**, 232 (1974).

<sup>456</sup> E. Campaigne and A. Dinner, *J. Med. Chem.* **13**, 1205 (1970).

<sup>457</sup> E. Campaigne, E. S. Neiss, C. C. Pfeiffer, and R. A. Beck, *J. Med. Chem.* **11**, 1049 (1968).

<sup>458</sup> K. Clarke, A. J. Humphries, and R. M. Scrowston, *J. Chem. Soc. C*, 1013 (1970).

<sup>459</sup> R. Neidlein and C. Gehringer, *Tetrahedron* **33**, 3233 (1977).

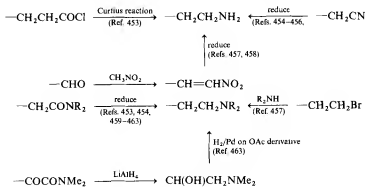
<sup>460</sup> N. B. Chapman, K. Clarke, B. A. Gore, A. Manolis, H. Porter, and T. M. Sutton, *J. C. S. Perkin I*, 750 (1973).

<sup>461</sup> N. B. Chapman, R. M. Scrowston, and T. M. Sutton, *J. C. S. Perkin I*, 3011 (1972).

<sup>462</sup> E. Campaigne, R. B. Rogers, A. Donelson, and T. R. Bosin, *J. Heterocycl. Chem.* **10**, 979 (1973).

<sup>463</sup> E. Campaigne and R. B. Rogers, *J. Heterocycl. Chem.* **10**, 297 (1973).

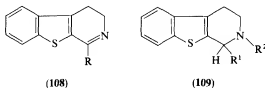
means, the sulfur analogs of 5-hydroxytryptamine,<sup>460,464</sup> 5,6-dihydroxytryptamine,<sup>462</sup> melatonin,<sup>456,465</sup> psilocin,<sup>455,459,461,463</sup> and bufotenine<sup>456</sup> have been prepared. Suitable protection of a hydroxy group in the benzenoid ring during the elaboration of the 3-side chain is of paramount importance.



SCHEME 5

## 2. Cyclic Amines

Reduced [1]benzothieno[2,3-*c*]pyridines (**109**) are of potential biological interest because the 3-CH<sub>2</sub>CH<sub>2</sub>N— side chain just described is now constrained in a ring, and of chemical interest as useful precursors of sulfur analogs of naturally occurring indole alkaloids.



Compounds **108** are generally prepared by Bischler–Napieralski cyclization (P<sub>2</sub>O<sub>5</sub>–POCl<sub>3</sub>) of benzo[*b*]thiophenes with a 3-CH<sub>2</sub>CH<sub>2</sub>NHCOR side chain.<sup>458,465–467</sup> They may be reduced by NaBH<sub>4</sub> to **109**, or dehydrogenated

<sup>464</sup> E. Campaigne and A. Dinner, *J. Pharm. Sci.* **58**, 892 (1969).

<sup>465</sup> E. Campaigne, E. Homfeld, and D. E. Mais, *J. Heterocycl. Chem.* **15**, 1351 (1978).

<sup>466</sup> T. R. Bosin, R. P. Maickel, A. Dinner, A. Snell, and E. Campaigne, *J. Heterocycl. Chem.* **9**, 1265 (1972).

<sup>467</sup> A. Shafiee and M. Mohammadpour-Toiserkani, *J. Heterocycl. Chem.* **16**, 653 (1979).

to the fully aromatic compound.<sup>458</sup> The reduced compounds **109** may also be prepared by Pictet–Spengler cyclization of 3-CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub> with RCHO and HCl.<sup>458</sup> 2-(3-Benzo[b]thienyl)ethylamine undergoes Pictet–Spengler cyclization with HCHO–HCO<sub>2</sub>H, to give **109** (R<sup>1</sup> = H, R<sup>2</sup> = Me).<sup>468</sup> Earlier, this was believed to be a normal *N,N*-dimethylation reaction; unusually, the reaction was reexamined because the product failed to show expected biological properties! The cyclic amide **109** (CHR<sup>1</sup> = C:O, R<sup>2</sup> = H) has been made by cyclization of the urethane, 3-CH<sub>2</sub>CH<sub>2</sub>NHCO<sub>2</sub>Et, with P<sub>2</sub>O<sub>5</sub>–POCl<sub>3</sub>.<sup>469</sup>

The compounds just described have been used as starting materials for the preparation of the sulfur analogs of dihydrorutecarpine, evodiamine,<sup>467</sup> rutecarpine,<sup>469</sup> yohimbane,<sup>470</sup> harmaline,<sup>465,466</sup> harmine,<sup>466</sup> and harman.<sup>458</sup>

The [3,2-*c*]pyridine isomers of **108** and **109** have been less widely studied. They may be prepared (sometimes with concomitant aromatization of the pyridine ring) by Bischler–Napieralski cyclization of a benzo[b]thiophene containing a 2-CH<sub>2</sub>CH<sub>2</sub>NHCOR side chain.<sup>458</sup> Amine **110**, of unspecified stereochemistry, has been made by condensation of 3-bromomethyl-5-chlorobenzo[b]thiophene with norephedrine and cyclization of the resulting 3-CH<sub>2</sub>NHCHMe·CH(OH)Ph compound with PPA.<sup>471</sup>

### 3. *α*-Amino Acids

Benzo[b]thiophene analogs **111** (R<sup>1</sup> = H, 5- or 6-R<sup>2</sup>) of substituted tryptophans have been prepared by reaction of a 5- or 6-substituted 3-chloromethylbenzo[b]thiophene with diethyl acetamido- or formamido-malonate, and hydrolysis of the product.<sup>456,472,473</sup> Corresponding *α*-methyl derivatives (**111**, R<sup>1</sup> = Me) may be obtained by the hydantoin route (Eq. 3).<sup>472</sup>

The L-isomer of **111** (R<sup>1</sup> = R<sup>2</sup> = H) has been obtained by enzymatic degradation of an appropriate DL-derivative.<sup>474,475</sup> In an interesting asymmetric synthesis, the imidazolinone **112** [L\* = (S)-1-phenylethyl] was

<sup>468</sup> E. Campaigne and E. Homfeld, *J. Heterocycl. Chem.* **16**, 1321 (1979).

<sup>469</sup> N. B. Chapman, C. G. Hughes, and R. M. Scrowston, *J. Chem. Soc. C*, 2269 (1970).

<sup>470</sup> G. Wolf, W. Meise, and F. Zymalkowski, *Tetrahedron Lett.*, 3223 (1972).

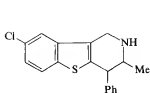
<sup>471</sup> Parcor, Japan. Kokai Tokkyo Koho 79/03,098 (1979) [*CA* **91**, 20476 (1979)].

<sup>472</sup> N. B. Chapman, R. M. Scrowston, and R. Westwood, *J. Chem. Soc. C*, 1855 (1969).

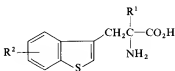
<sup>473</sup> R. L. Titus and C. F. Titus, *J. Heterocycl. Chem.* **10**, 679 (1973).

<sup>474</sup> H. M. Rajh, J. H. Uitzetter, L. W. Westerhuis, C. L. Van den Dries, and G. I. Tesser, *Int. J. Pept. Protein Res.* **14**, 68 (1979).

<sup>475</sup> Y. Yabe, C. Miura, H. Horikoshi, and Y. Baba, *Chem. Pharm. Bull.* **24**, 3149 (1976).



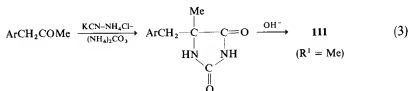
(110)



(111)



(112)



Ar = 3-benzo[*b*]thienyl

alkylated with 3-bromomethylbenzo[*b*]thiophene, then the product was hydrolyzed, to give the  $\alpha$ -methyl amino acid (111, R<sup>1</sup> = Me, R<sup>2</sup> = H) in a state of high optical purity.<sup>476</sup>

### I. HYDROXYBENZO[*b*]THIOPHENES

2- and 3-Hydroxybenzo[*b*]thiophenes are considered as their oxo tautomers in Section IV,B.

#### 1. Preparation

4-Hydroxybenzo[*b*]thiophene is conveniently obtained by the dehydrogenation of ketone 68.<sup>292</sup> 4-, 5-, and 6-Methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic acids are obtained from the appropriate  $\beta$ -aryl- $\alpha$ -mercaptoacrylic acid (Ref. 2, p. 233) by cyclization with chlorine<sup>477</sup>; the reaction is cleaner than with iodine, but some ring chlorination may also occur.<sup>247</sup> The methoxy

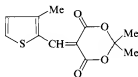
<sup>476</sup> U. Schöllkopf, H. H. Hausberg, I. Hoppe, M. Segal, and U. Reiter, *Angew. Chem., Int. Ed. Engl.* **17**, 117 (1978).

<sup>477</sup> P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *Tetrahedron* **25**, 2781 (1969).

acids are converted into the corresponding phenols by conventional means.

3-Methylthiophene-2-carboxaldehyde condenses with isopropylidene malonate and the product **113** undergoes flash pyrolysis (500°C at low pressure), to give 5-hydroxybenzo[*b*]thiophene (96%).<sup>478</sup> 6-Hydroxy-2-methylbenzo[*b*]thiophene is formed similarly (98%).

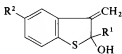
The thieno[2,3-*c*]pyrylium salt **114** undergoes ring opening/ring closure on treatment with alkali, to give a 6-R-substituted 7-hydroxy-5-methylbenzo[*b*]thiophene.<sup>479</sup> 7-Hydroxy-3-methylbenzo[*b*]thiophene may be prepared from the corresponding 7-chloro compound, either by oxygenation of the derived Grignard reagent (50%), or by direct treatment with NaOH at ~290°C (63%).<sup>250</sup> 7-Hydroxybenzo[*b*]thiophene is perhaps most conveniently prepared by conventional routes from 2-mercapto-3-methoxybenzaldehyde; the latter is readily obtained from commercially available orthovanillin (2-hydroxy-3-methoxybenzaldehyde).<sup>480</sup>



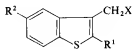
(113)



(114)



(115)



(116)

## 2. Substitution Reactions

These are summarized in Table III.<sup>244-249,459,481-483</sup>

<sup>478</sup> G. J. Baxter, R. F. C. Brown, and G. L. McMullen, *Aust. J. Chem.*, **27**, 2605 (1974).

<sup>479</sup> V. I. Dulencko, I. G. Katts, L. V. Dulencko, and G. N. Dorofeenko, *Khim. Geterotsikl. Soedin.*, 134 (1970).

<sup>480</sup> R. M. Scrowston and L. K. A. Rahman, unpublished work (1979).

<sup>481</sup> P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *J. Chem. Soc. C*, 1 (1969).

<sup>482</sup> S. M. A. D. Zayed, M. M. Sidky, and A. Emran, *J. Prakt. Chem.*, **315**, 244 (1973).

<sup>483</sup> B. D. Tilak and A. M. Malte, *Indian J. Chem.*, **7**, 1173 (1969).

TABLE III. SUBSTITUTION REACTIONS OF HYDROXYBENZO[*b*]THIOPHENES<sup>a</sup>

Substituent(s)	Products							Ref.
	Bromination <sup>b</sup>	Nitration	Formylation	Friedel-Crafts acylation	Fries rearrangement	Claisen rearrangement	Other reactions	
4-OH	5,7-Br <sub>2</sub> 5-Br (NBS)	5- and 7-NO <sub>2</sub>	5-CHO <sup>c</sup>		4-OH, 7-Ac, and 2,3-H <sub>2</sub> , 4-OH, 7-Ac	5-allyl		246, 248
4-OH, 3-Me	5,7-Br <sub>2</sub> 5-Br (NBS)	5- and 7-NO <sub>2</sub>	5-CHO <sup>c</sup>		4-OH, 7-Ac, and 4-OH, 2-Ac	5-allyl		248
4-OMe	7-Br	7-NO <sub>2</sub>	7-CHO <sup>d</sup>	7-Ac				246, 247
4-OCOPh	3-Br	7-NO <sub>2</sub>	unreactive <sup>d</sup> 3-CHO (Rieche)	7-Ac				246, 459
4-OMe, 3-Me	2- and 7-Br (also with NBS)	2- and 7-NO <sub>2</sub>	2- and 7-CHO <sup>d</sup>	2- and 7-Ac				247

4-OCH <sub>2</sub> Ph	7-Br					7-I [I <sub>2</sub> + Hg(II) oxide] 4-CH <sub>2</sub> NR <sub>2</sub> (Mannich)	459  481, 482
5-OH			4-CHO <sup>c</sup>				
5-OH, 3-Me	4-Br	4-NO <sub>2</sub>	4-CHO <sup>c</sup>		5-OH, 2-Ac <sup>c</sup>	4-allyl	481
6-OH	7-Br, 2,7-Br <sub>2</sub> , and 5,7-Br <sub>2</sub>		7-NO <sub>2</sub> , 5-NO <sub>2</sub> , and 2-NO <sub>2</sub>			7-allyl	244
6-OMe				2-COEt			483
6-OMe, 3-Me	2-Br (NBS)			2-Ac			245
7-OH, 3-Me	6-Br and 4-Br (NBS)	6-NO <sub>2</sub> , 4,6-diNO <sub>2</sub> , and 3-Me 4,7-quinone	6-CHO <sup>c</sup>		7-OH, 2-Ac	6-allyl	249

<sup>a</sup> Earlier work is discussed in Ref. 2 (p. 308). <sup>b</sup> With molecular bromine, unless stated otherwise. <sup>c</sup> Gattermann reaction. <sup>d</sup> Vilsmeier-Haack. <sup>e</sup> Contrast 5-hydroxybenzo[*b*]thiophene, which gives 5-OH, 4-Ac (Ref. 2, p. 308).



## J. DERIVATIVES WITH A HYDROXYL GROUP IN A SIDE CHAIN

2-Hydroxymethylbenzo[*b*]thiophene and its methyl ether are obtained in high yield by treatment of the 1,2-dibromo compound **81** ( $X = \text{Br}$ ,  $n = 1$ ) with aqueous acetone and methanol, respectively.<sup>484</sup> Heating aryl prop-2-ynyl sulfoxides,  $\text{R}^1\text{C}\equiv\text{CCH}_2\text{SOC}_6\text{H}_4\cdot\text{R}^2$ -*p*, with  $\text{XH}$ , produces compounds **116** ( $X = \text{OEt}$ ,  $\text{OH}$ ,  $\text{OAc}$ ,  $\text{SPh}$ ) in high yield, via intermediate **115**.<sup>485,486</sup>

Nitration of 2-acetoxymethylbenzo[*b*]thiophene gives a mixture of the 3- and 6-nitro products and not just the 3-isomer as previously reported (Ref. 2, p. 314).<sup>487</sup>

K. BENZO[*b*]THIOPHENEQUINONES1. Benzo[*b*]thiophene-2,3-quinones

These undergo base-catalyzed ring opening with  $\text{PhCHCl}\cdot\text{CO}_2\text{H}$ , and the resulting  $\alpha$ -ketoacids **117** can be cyclized, to give 2-phenylbenzo[*b*]thiophene-3-carboxylic acids.<sup>488,489</sup> The 3-oxime of a substituted benzo[*b*]thiophene-2,3-quinone gives the corresponding 1,2-benzisothiazole-3-carboxylate anion (85%) on treatment with base.<sup>490</sup> Oxidation of the 3-semicarbazone with lead(IV) acetate gives 3-diazobenzo[*b*]thiophene-2-one (**58**;  $X = \text{N}_2$ ).<sup>491</sup>

Benzo[*b*]thiophene-2,3-quinones can be reduced in DMSO by *t*-BuOK or by the enolate anion of propiophenone to the radical-anion; this is responsible for the lability of a 5-halogeno substituent in the presence of a nucleophile.<sup>492,493</sup> On treatment with a Grignard reagent, a benzo[*b*]thiophene-2,3-quinone gives the expected 2,3-diol, which undergoes the pinacolone rearrangement, to give the 3,3-disubstituted thiooxindole.<sup>494</sup>

<sup>484</sup> W. D. Cotterill, C. J. France, R. Livingstone, J. R. Atkinson, and J. Cottam, *J. C. S. Perkin I*, 787 (1972).

<sup>485</sup> Y. Makisumi and S. Takada, *J. C. S. Chem. Commun.*, 848 (1974).

<sup>486</sup> T. Numata, O. Itoh, and S. Oae, *Chem. Lett.*, 909 (1977).

<sup>487</sup> V. P. Mamaev and O. P. Shkurko, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 122 (1967) [*CA* **69**, 106388 (1968)].

<sup>488</sup> F. Sauter and A. Dzerovicz, *Monatsh. Chem.* **100**, 899 (1969).

<sup>489</sup> F. Sauter and A. Dzerovicz, *Monatsh. Chem.* **101**, 1806 (1970).

<sup>490</sup> H. Newman and R. B. Angier, *J. Org. Chem.* **34**, 3484 (1969).

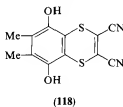
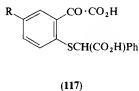
<sup>491</sup> D. Daniil, U. Merkle, and H. Meier, *Syntheses*, 535 (1978).

<sup>492</sup> F. Ciminale, G. Bruno, L. Testaferri, M. Tiecco, and G. Martelli, *J. Org. Chem.* **43**, 4509 (1978).

<sup>493</sup> G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer, and R. Blankespoor, *J. Am. Chem. Soc.* **92**, 2762 (1970).

<sup>494</sup> M. M. M. Sallam, M. H. Elnagdi, and M. H. Abdel-Hady, *Helv. Chim. Acta* **58**, 1940 (1975).

In the PE spectrometer at 780°C, the thiolactone **60** ( $XY = :O$ ) can be detected as one of the intermediates in the decomposition of the parent quinone.<sup>495</sup> Conventional thermolysis gives a complex range of products.<sup>496</sup>



## 2. Benzo[b]thiophene-4,7-quinones

These quinones may be prepared by oxidation of the corresponding 7-hydroxy compound with Fremy's salt; the presence of a 3-phenyl group hinders oxidation in the 4-position, with the result that a 6,7-quinone is then also formed.<sup>497,498</sup> Anodic oxidation of a 5-substituted 4-methoxybenzo[b]thiophene in boiling methanol gives the 4,7-bisacetal, acidic hydrolysis of which gives the corresponding 4,7-quinone.<sup>499</sup> 2,3-Dichloro-5,6-dimethyl-*p*-benzoquinone reacts with  $\text{NaS}\cdot\text{C}(\text{CN})=\text{C}(\text{CN})\cdot\text{SNa}$ , to give the 1,4-benzodithiin **118**. Per-acid oxidation of **118** or, better, of the corresponding quinone, gives 2,3-dicyano-5,6-dimethylbenzo[b]thiophene-4,7-quinone.<sup>500,501</sup>

A 5-(methylthio)-6-( $\text{C}_{30}\text{H}_{61}$ )-benzo[b]thiophene-4,7-quinone has been isolated from cultures of an extremely thermophilic and acidophilic micro-organism.<sup>502</sup> In connection with the structure determination of this natural product, 5-bromo-6-methylbenzo[b]thiophene-4,7-quinone was treated with  $\text{MeS}^-$ , to give mainly the 5-SMe derivative. Unexpectedly, a minor product from this reaction was the 5-SMe, 6- $\text{CH}_2\text{SMe}$  compound, formed by both nuclear and side-chain methylthiolation.<sup>503</sup>

<sup>495</sup> R. Schulz and A. Schweig, *Tetrahedron Lett.*, 59 (1979).

<sup>496</sup> O. Tsuge, M. Tashiro, S. Kanemasa, and K. Takasaki, *Chem. Lett.*, 827 (1972).

<sup>497</sup> H. Ishii, R. Ohtake, H. Ohida, H. Mitsui, and N. Ikeda, *Yakugaku Zasshi* **90**, 1283 (1970) [*CA* **74**, 3444 (1971)].

<sup>498</sup> H. Ishii, T. Hanaoka, H. Sugano, and N. Ikeda, *Yakugaku Zasshi* **90**, 1290 (1970) [*CA* **74**, 12918 (1971)].

<sup>499</sup> B. L. Chenard and J. S. Swenton, *J. C. S. Chem. Commun.*, 1172 (1979).

<sup>500</sup> K. Fickentscher, *Chem. Ber.*, **103**, 3000 (1970).

<sup>501</sup> K. Fickentscher, *Chem. Ber.*, **102**, 2378 (1969).

<sup>502</sup> M. De Rosa, S. De Rosa, A. Gambacorta, L. Minale, R. H. Thomson, and R. D. Worthington, *J. C. S. Perkin I*, 653 (1977).

<sup>503</sup> R. H. Thomson and R. D. Worthington, *J. C. S. Perkin I*, 282 (1980).

## L. ALDEHYDES AND KETONES

## 1. Aldehydes

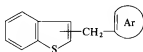
a. *Preparation.* Long-established methods continue to be used widely.<sup>2</sup> Methods involving metallation reactions will be mentioned in Section V. Benzo[*b*]thiophene-2-carboxaldehyde is obtained (80%) by the oxidation of the readily available 2*H*-1-benzothiopyran (**119**) with SeO<sub>2</sub>-DMF.<sup>504</sup> 3-Arylbenzo[*b*]thiophene-2-carboxaldehydes are obtained by oxidation of the 4-aryl-1-benzothiopyrylium perchlorates (**120**; Ar<sup>2</sup> = H) with MnO<sub>2</sub>; similar treatment of the 2,4-diaryl salt gives the corresponding ketone (2-COAr<sup>2</sup>).<sup>505</sup>



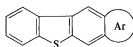
(119)



(120)



(121)



(122)

Oxidation of 3-hydroxymethylbenzo[*b*]thiophene with silver carbonate on celite gives the 3-aldehyde (70%).<sup>506</sup> Controlled treatment of a 3-methyl- or 3-chloromethylbenzo[*b*]thiophene with *N*-bromosuccinimide gives the —CHBr<sub>2</sub> and —CHBrCl compound, which can be hydrolyzed to the 3-aldehyde in very high yield with aqueous sodium carbonate.<sup>187,350</sup> If, however, the 2-position is free, some 2-bromo compound may also be formed.<sup>507</sup>

Benzo[*b*]thiophene undergoes selective Rieche formylation (65%) in the 3-position with dichloromethyl butyl ether and TiCl<sub>4</sub>.<sup>508</sup> 2-Bromo- and 3-methylbenzo[*b*]thiophene are similarly formylated in the vacant thiophene position.<sup>345,508</sup> The diarylmethane compounds **121** (Ar = thiophene, benzo[*b*]thiophene, or benzene) undergo Rieche formylation, but the resulting aldehyde cyclizes under the conditions of the reaction, to give the annelated products **122**.<sup>509</sup>

<sup>504</sup> A. Ruwet, J. Meessen, and M. Renson, *Bull. Soc. Chim. Belg.* **78**, 459 (1969).

<sup>505</sup> I. Degani and R. Fochi, *Ann. Chim. (Rome)* **58**, 251 (1968).

<sup>506</sup> M. Fétizon, F. Gomez-Parra, and J.-M. Louis, *J. Heterocycl. Chem.* **13**, 525 (1976).

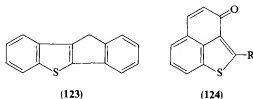
<sup>507</sup> H. J. Brabander, *J. Heterocycl. Chem.* **10**, 127 (1973).

<sup>508</sup> N. P. Buu-Hoi, A. Croisy, and P. Jacquignon, *J. Chem. Soc. C*, 339 (1969).

<sup>509</sup> M. Ahmed, J. Ashby, M. Ayad, and O. Meth-Cohn, *J. C. S. Perkin I*, 1099 (1973).

b. *Reactions.* Benzo[*b*]thiophene-3-carboxaldehyde is nitrated under various conditions, in all except the 2-position.<sup>240</sup>

Benzo[*b*]thiophene-2,3-dicarboxaldehyde reacts with hydrazine, to give [1]benzothieno[2,3-*d*]pyridazine (**33**; X = H).<sup>510</sup> A range of other 2,3-dicarbonyl compounds gives analogous products with hydrazine or substituted hydrazines.<sup>510,511</sup> The *p*-toluenesulfonylhydrazine of 2-phenylbenzo[*b*]thiophene-3-carboxaldehyde undergoes the Bamford–Stevens reaction with NaOEt, to give the indenobenzothiophene **123**.<sup>512</sup>



## 2. Ketones

a. *Preparation.* Ketones are generally prepared by the methods discussed in Ref. 2. A new, high yield, one-pot synthesis of 3-acetylbenzo[*b*]thiophenes from a benzenethiol is of interest because the product is not contaminated with the 2-acetyl isomer (contrast Friedel–Crafts acylation). It involves conversion of the benzenethiol into **115** ( $R^1 = CH_2OAr$ ) (cf. Section IV,J), which gives the 5-substituted 3-acetyl compound on successive treatment with alkali and acetic acid.<sup>513,514</sup>

When a 2-alkylbenzo[*b*]thiophene undergoes Friedel–Crafts acylation with  $AlCl_3$ –cinnamoyl chloride, the resulting 3-ketone cyclizes spontaneously into the 4-position with loss of benzene to give the cyclic ketone **124**.<sup>515</sup> With 2-bromobenzo[*b*]thiophene, a similar reaction gives a mixture of **124** [ $R = Cl$  (*sic*)] and the 2-Br, 3- $COCH_2CHPh_2$  substituted benzo[*b*]thiophene derivative; with 2-methoxybenzo[*b*]thiophene, the ether is demethylated to give **124** ( $R = OH$ ).<sup>516</sup> The formation of other cyclic ketones by intramolecular cyclization of carboxylic acids will be considered in Section IV,M.

b. *Substitution Reactions.* Nitration of 3-acetylbenzo[*b*]thiophene in hot acetic acid gives mainly di(3-benzo[*b*]thenoyl)furoxan; the 3-acetyl-2-methyl and 2-acetyl-3-methyl derivatives behave similarly, and also undergo

<sup>510</sup> G. Doré, M. Bonhomme, and M. Robba, *Tetrahedron* **28**, 2553 (1972).

<sup>511</sup> G. Doré, M. Bonhomme, and M. Robba, *Bull. Soc. Chim. Fr.*, 4629 (1972).

<sup>512</sup> B. Iddon, H. Suschitzky, and D. S. Taylor, *J. C. S. Perkin I*, 2505 (1974).

<sup>513</sup> K. C. Majumdar and B. S. Thyagarajan, *J. C. S. Chem. Commun.*, 83 (1972).

<sup>514</sup> K. C. Majumdar and B. S. Thyagarajan, *Int. J. Sulfur Chem., Part A* **2**, 67 (1972).

<sup>515</sup> R. Neidlein and K. F. Cepera, *Justus Liebigs Ann. Chem.*, 627 (1978).

<sup>516</sup> R. Neidlein and L. Seguil-Camargo, *Justus Liebigs Ann. Chem.*, 965 (1979).

some displacement of the acetyl group by a nitro group.<sup>240,252</sup> When treated with  $\text{KNO}_3\text{--H}_2\text{SO}_4$  at  $0^\circ\text{C}$  or with  $\text{AcOH--Ac}_2\text{O--HNO}_3$  at  $0^\circ\text{C}$ , 3-acetylbenzo[*b*]thiophene is nitrated in all positions in the benzene ring, but not in the 2-position.<sup>240</sup>

## M. CARBOXYLIC ACIDS

### 1. Preparation

a. *2-Carboxylic Acids.* Substituted cinnamic acids react with thionyl chloride in pyridine, to give (after hydrolysis of the carbonyl chloride) the 3-chlorobenzo[*b*]thiophene-2-carboxylic acids **125** ( $\text{X} = \text{Cl}$ ).<sup>517-520</sup> By starting from  $\text{ArCH=CHR}$  ( $\text{R} = \text{CHO}$ ,  $\text{Ph}$ ,  $\text{CN}$ , etc.), the reaction can be extended to include the preparation of 3-chlorobenzo[*b*]thiophene with a range of 2-R substituents.<sup>521</sup> Hydrocinnamic acid and its  $\beta$ -phenyl and  $\beta$ -methyl derivatives give **125** ( $\text{X} = \text{Cl}$ ,  $\text{Ph}$ , and  $\text{Me}$ , respectively), but the yield of the last is increased if the intermediate,  $\text{PhCHMe}\cdot\text{CCl}(\text{SCl})\cdot\text{COCl}$ , is cyclized with  $\text{AlCl}_3$ .<sup>517,522</sup> Alkynes,  $\text{ArC}\equiv\text{CCO}_2\text{H}$ , react with  $\text{HBr--SO}_2$ , to give the 3-bromo acids **125** ( $\text{X} = \text{Br}$ ).<sup>523,524</sup> or with thionyl chloride, to give (after hydrolysis) the 3-chloro acid **125** ( $\text{X} = \text{Cl}$ ).<sup>525</sup> Ethyl phenylpropionate,  $\text{PhC}\equiv\text{CCO}_2\text{Et}$ , undergoes addition of  $\text{S}_2\text{Cl}_2$ , then the product is oxidized with peroxyacetic acid, to give the 1,1-dioxide of **125** ( $\text{R} = \text{H}$ ,  $\text{X} = \text{Cl}$ ; ethyl ester).<sup>526</sup> Arenethiols undergo addition to  $\text{R'O}_2\text{CC}\equiv\text{CCO}_2\text{R'}$ , then the products cyclize under mild conditions to give the diester of the 2,3-diacid **125** ( $\text{X} = \text{CO}_2\text{H}$ ).<sup>527</sup>

The *o*-(methylthio)styrene derivatives **126** ( $\text{R}^2 = \text{CO}_2\text{H}$ ,  $\text{COMe}$ , or  $\text{Me}$ ) react successively with  $\text{SO}_2\text{Cl}_2$  and pyridine, to give the appropriate 3-R<sup>3</sup>-substituted benzo[*b*]thiophene-2-carboxylic acid (or the 2-COMe or 2-Me benzo[*b*]thiophene).<sup>528</sup>

<sup>517</sup> T. Higa and A. J. Krubsack, *J. Org. Chem.* **41**, 3399 (1976).

<sup>518</sup> W. B. Wright and H. J. Brabander, *J. Heterocycl. Chem.* **8**, 711 (1971).

<sup>519</sup> T. Higa and A. J. Krubsack, *J. Org. Chem.* **40**, 3037 (1975).

<sup>520</sup> A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 125 (1973).

<sup>521</sup> S. Nakagawa, J. Okumura, F. Sakai, H. Hoshi, and T. Naito, *Tetrahedron Lett.*, 3719 (1970).

<sup>522</sup> A. J. Krubsack and T. Higa, *Tetrahedron Lett.*, 5149 (1968).

<sup>523</sup> I. V. Smirnov-Zamkov and Yu. L. Zborovskii, *J. Org. Chem. USSR (Engl. Transl.)* **11**, 1784 (1975).

<sup>524</sup> I. V. Smirnov-Zamkov and Yu. L. Zborovskii, *Zh. Org. Khim.* **13**, 667 (1977).

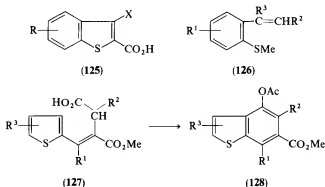
<sup>525</sup> C. M. Bonnin, P. A. Cadby, C. G. Freeman, and A. D. Ward, *Aust. J. Chem.* **32**, 833 (1979).

<sup>526</sup> W. Ried and W. Ochs, *Chem. Ber.* **107**, 1334 (1974).

<sup>527</sup> K. Undheim and R. Lie, *Acta Chem. Scand.* **27**, 595 (1973).

<sup>528</sup> A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.* **79**, 593 (1970).

The easily obtained  $\beta$ -keto ester derivatives,  $\text{MeCOCH}(\text{SAr})\text{CO}_2\text{Me}$ , undergo photocyclization to a 3-methylbenzo[*b*]thiophene-2-carboxylic ester.<sup>529</sup>



b. *Other Carboxylic Acids.* A patent describes the direct conversion of 3-methylbenzo[*b*]thiophene into the 3-carboxylic acid by oxygen in the presence of  $\text{Co}(\text{OAc})_2$ .<sup>530</sup>

Thiophene-2-aldehydes or 2-ketones undergo the Stobbe reaction, and the products **127** are cyclized by  $\text{Ac}_2\text{O}-\text{NaOAc}$  to the 6-carboxylic esters **128**.<sup>531-536</sup>

## 2. Reactions

a. *Electrophilic Substitution.* Under two sets of nitration conditions, benzo[*b*]thiophene-2-carboxylic acid undergoes substitution in all except the 5-position.<sup>242</sup> The corresponding 3-methyl and 3-*t*-butyl derivatives show a similar substitution pattern except that, for the former, nitrode-carboxylation, and for the latter, protode-*t*-butylation (leading to nitration products of benzo[*b*]thiophene-2-carboxylic acid) and nitrode-*t*-butylation become significant processes.<sup>74,242</sup> It is somewhat surprising that Russian workers have been able to use the nitration of benzo[*b*]thiophene-2-carboxylic acid as a preparative route for the 4-nitro derivative.<sup>487</sup> As with

<sup>529</sup> T. Sasaki and K. Hayakawa, *Tetrahedron Lett.* **21**, 1525 (1980).

<sup>530</sup> S. M. Maksimov and N. A. Kazbulatova, USSR Patent 194,809 (1967) [*CA* **69**, 19009 (1968)].

<sup>531</sup> S. M. Abdel-Wahhab and N. R. El-Rayyes, *J. Prakt. Chem.* **313**, 247 (1971).

<sup>532</sup> N. R. El-Rayyes, *J. Prakt. Chem.* **315**, 300 (1973).

<sup>533</sup> N. R. El-Rayyes and N. A. Al-Salman, *J. Prakt. Chem.* **317**, 552 (1975).

<sup>534</sup> N. R. El-Rayyes and N. A. Al-Salman, *J. Heterocycl. Chem.* **13**, 285 (1976).

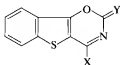
<sup>535</sup> H. H. Moussa and D. Zaki, *Indian J. Chem., Sect. B* **15**, 555 (1977).

<sup>536</sup> S. M. Abdel-Wahhab and N. R. El-Rayyes, *J. Chem. Soc. C*, 3171 (1971).

other benzo[*b*]thiophenes containing an electron-withdrawing 3-substituent, benzo[*b*]thiophene-3-carboxylic acid resists nitration in the 2-position, but is substituted in all other positions.<sup>241</sup>  $\beta$ -(3-Benzo[*b*]thienyl)propionic acid substitutes normally in the 2-position.<sup>537,538</sup>

**b. Intramolecular Cyclizations.** There are numerous examples of the intramolecular cyclization of acids of the type  $-(CH_2)_nCO_2H$  to the corresponding cyclic ketones. Cyclization from the 2- to the 3-position in benzo[*b*]thiophene, or vice versa, has given 5-,<sup>2</sup> 6-,<sup>2</sup> 7-,<sup>539</sup> and 16-membered ring ketones.<sup>540</sup> If the 2-position is blocked, 3- $(CH_2)_nCO_2H$  and related derivatives will cyclize into the 4-position<sup>537,538,541,542</sup>; if the 5-position is blocked, a 4- $CH_2CH_2CO_2H$  group will cyclize into the 3-position.<sup>543</sup> 3-Phenylbenzo[*b*]thiophene-2-carbonyl chloride is cyclized by  $AlCl_3$  on to the phenyl substituent; PPA on the corresponding acid gives a rearranged product.<sup>544,545</sup>

**c. Other Reactions.** The rates of alkaline hydrolysis of methyl carboxylates in 70% dioxane decrease in the sequence 3-benzo[*b*]furanyl > 2-benzo[*b*]furanyl > 2-benzo[*b*]thienyl > 3-benzo[*b*]thienyl.<sup>546</sup> 3-Hydroxybenzo[*b*]thiophene-2-amidines or -2-imidates<sup>547</sup> are cyclized by  $C=Y$  (e.g.,  $N,N'$ -dicarbonyldiimidazole or thiophosgene), to give the oxazine derivatives **129** ( $X = OR$  or  $N<$ ,  $Y = O$  or  $S$ ).<sup>548</sup>  $\alpha$ -Methoxy-(2-benzo[*b*]thienyl)acetic acid undergoes an allylic-type rearrangement when treated with  $HBr-AcOH$ , to give (3-bromo-2-benzo[*b*]thienyl)acetic acid;  $\alpha$ -



(129)

<sup>537</sup> E. Campaigne and D. R. Knapp, *J. Heterocycl. Chem.* **7**, 107 (1970).

<sup>538</sup> R. Neidlein and H. Seel, *Angew. Chem., Int. Ed. Engl.* **15**, 775 (1976).

<sup>539</sup> P. Cagniant and G. Kirsch, *C. R. Acad. Sci., Ser. C* **272**, 948 (1971).

<sup>540</sup> C. Galli, G. Illuminati, and L. Mandolini, *J. Org. Chem.* **45**, 311 (1980).

<sup>541</sup> R. Neidlein and N. Kolb, *Arch. Pharm. (Weinheim, Ger.)* **312**, 338 (1979).

<sup>542</sup> R. Neidlein and M. H. Salzl, *J. Chem. Res. (S)*, 118; (*M*), 1466 (1977).

<sup>543</sup> R. Neidlein and G. Humburg, *Justus Liebigs Ann. Chem.*, 904 (1977).

<sup>544</sup> F. Sauter and A. Dzerovicz, *Monatsh. Chem.* **100**, 913 (1969).

<sup>545</sup> F. Sauter and W. Deinhammer, *Monatsh. Chem.* **101**, 544 (1970).

<sup>546</sup> A. Feinstein, P. H. Gore, and G. L. Reed, *J. Chem. Soc. B*, 205 (1969).

<sup>547</sup> P. Stoss, M. Herrmann, and G. Satzinger, *Ger. Offen.* 2,258,036 (1974) [*CA* **81**, 49560 (1974)].

<sup>548</sup> P. Stoss, *Chem. Ber.* **111**, 314 (1978).

methoxy-(3-benzo[b]thienyl)acetic acid undergoes the expected overall conversion of —OMe into —Br.<sup>549</sup>

## N. SULFONIC ACIDS

Most recent publications on the sulfonation of benzo[b]thiophenes confirm existing knowledge.<sup>1,2</sup> Benzo[b]thiophene and its 5-bromo and 7-chloro derivatives undergo sulfonation ( $\text{H}_2\text{SO}_4\text{--Ac}_2\text{O}$ ) in the 3-position.<sup>550</sup> 3-Methylbenzo[b]thiophene 1,1-dioxide is chlorosulfonated in the 2-position<sup>551</sup>; the apparent absence of substitution in the 6-position is unusual for a 1,1-dioxide.

3-Bromobenzo[b]thiophene-2-sulfonamide may be obtained in a single step by treating  $\text{PhC}\equiv\text{CSO}_2\text{NH}_2$  with HBr and  $\text{SO}_2$ .<sup>552</sup>

Benzo[b]thiophene-3-sulfonyl chloride is reduced to the sulfinic acid by  $\text{Na}_2\text{SO}_3\text{--NaHCO}_3$ .<sup>101</sup>

## O. DERIVATIVES WITH SULFUR OR SELENIUM IN A SIDE CHAIN

### 1. Sulfur Derivatives

Benzo[b]thiophenethiols are obtained by the general methods discussed previously (Ref. 2, p. 351). Attempted reduction of substituted benzo[b]thiophene-3-sulfonyl chlorides with  $\text{Zn--H}_2\text{SO}_4$ , according to an established procedure, gave only the benzo[b]thiophene; reduction with  $\text{LiAlH}_4$ , however, gave the 3-thiols ( $\sim 90\%$ ).<sup>550</sup> Thioindoxyl reacts with the mercaptoacids,  $\text{HS}(\text{CH}_2)_n\text{CO}_2\text{H}$ , to give the benzo[b]thiophene-3-sulfides,  $3\text{-S}(\text{CH}_2)_n\text{CO}_2\text{H}$ .<sup>553</sup>

The latter are cyclized into the 2-position by conventional methods, to give thiopyran derivatives ( $n = 2$ ) or their 7-membered analogs ( $n = 3$ ).<sup>553,554</sup> If the 2-position is occupied, cyclization takes place into the 4-position.<sup>555</sup> Similar cyclizations take place from the 2- into the 3-position, and from the

<sup>549</sup> S. Gronowitz, J. Rehnö, and J. Sandström, *Acta Chem. Scand.* **24**, 304 (1970).

<sup>550</sup> N. B. Chapman, C. G. Hughes, and R. M. Scrowston, *J. Chem. Soc. C*, 2431 (1970).

<sup>551</sup> I. U. Numanov, N. R. Radzhabov, and I. M. Nasyrov, *Dokl. Akad. Nauk Tadzh. SSR* **16**, 43 (1973).

<sup>552</sup> I. V. Smirnov-Zamkov, Yu. L. Zborovskii, and V. I. Staninets, *Zh. Org. Khim.* **15**, 1782 (1979).

<sup>553</sup> F. Lepage, P. Cagniant, and D. Cagniant, *Bull. Soc. Chim. Fr.*, 3107 (1973).

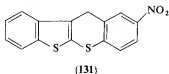
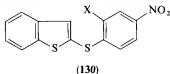
<sup>554</sup> P. Cagniant and J. Trierweiler, *Bull. Soc. Chim. Fr.*, 596 (1969).

<sup>555</sup> J. F. Muller, D. Cagniant, and P. Cagniant, *Tetrahedron Lett.*, 81 (1972).



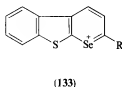
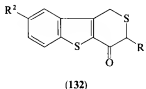
7- into the 6-position.<sup>249,556</sup> Benzo[*b*]thiophene-2- and 3-thiols condense with chloroacetaldehyde diethyl acetal or chloroacetone, and the resulting sulfides are cyclized by PPA to give derivatives of thieno[2,3-*b* or 3,2-*b*][1]benzothiophene (e.g., **102**, X = S, Y = Z = CH from 3-SH).<sup>550</sup>

The [1]benzothieno[2,3-*b*][1]benzothiopyran (**131**) is obtained by Bamford-Stevens reduction of the *p*-toluenesulfonylhydrazone of aldehyde **130** (X = CHO), by cyclization of the aldehyde **130** (X = CHO) with POCl<sub>3</sub> and reduction of the resulting thiopyrylium salt with NaBH<sub>4</sub>, or by pyrolysis of the diazomethane derivative **130** (X = CHN<sub>2</sub>).<sup>557</sup>



Benzo[*b*]thiophene-2-thiol reacts with pyrrolidine or morpholine, to give 2-pyrrolidino- or 2-morpholinobenzo[*b*]thiophene (~80%).<sup>558</sup>

The acids, ArCH<sub>2</sub>SCHR<sup>1</sup>·CO<sub>2</sub>H (Ar = 3-benzo[*b*]thienyl), obtained from ArCH<sub>2</sub>SH in the usual way, may be cyclized to the 2-benzothiopyrans **132** (R<sup>1</sup> = H or alkyl, R<sup>2</sup> = H).<sup>559</sup> The β-keto ester **132** (R<sup>1</sup> = CO<sub>2</sub>R, R<sup>2</sup> = NO<sub>2</sub>) is obtained in a single step by treatment of ω-bromo-2-chloro-5-nitroacetophenone with HSCH<sub>2</sub>CO<sub>2</sub>R (2 mol equiv) in the presence of NaOR.<sup>560</sup>



## 2. Selenium Derivatives

Most selenium-substituted benzo[*b*]thiophenes are obtained by metallation reactions (Section V). 2-Bromobenzo[*b*]thiophene-3-carboxaldehyde (and the 3-Br, 2-CHO isomer) reacts with selenourea, to give the correspond-

<sup>556</sup> P. Cagniant and G. Kirsch, *C. R. Acad. Sci., Ser. C* **272**, 406 (1971).

<sup>557</sup> B. Iddon, H. Suschitzky, D. S. Taylor, and K. E. Chippendale, *J. C. S. Perkin I*, 2500 (1974).

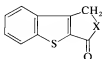
<sup>558</sup> S. Scheithauer, H. Hartmann, and R. Mayer, *Z. Chem.* **8**, 181 (1968).

<sup>559</sup> P. Cagniant, *C. R. Acad. Sci., Ser. C* **271**, 1086 (1970).

<sup>560</sup> R. M. Scrowston and D. C. Shaw, *J. C. S. Perkin I*, 749 (1976).

ing 2- or 3-SeH compound.<sup>561</sup> Di(2-benzo[b]thienyl) diselenide, from 2-bromobenzo[b]thiophene and selenium, reacts with  $\beta$ -chloropropionic acid to give the 2-SeCH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>H compound, which can be cyclized into the 3-position with P<sub>2</sub>O<sub>5</sub>. Successive treatment of the resulting ketone with NaBH<sub>4</sub>, Ac<sub>2</sub>O, and trityl perchlorate gives the seleninium salts **133** (R = H).<sup>562</sup> Salts **65** (X = Se, R<sup>1</sup> = R<sup>2</sup> = H) are formed similarly. In an alternative approach to these salts, 2-(methylseleno)benzo[b]thiophene undergoes Friedel-Crafts acetylation, then the benzylidene derivative of the resulting 3-Ac, 2-SeMe compound is cyclized, reduced, and aromatized to give **133** (R = Ph).<sup>563</sup> Seleno[3,2-b][1]benzothiophene-2-carboxylic acid (or ester) (**102**; X = Se, Y = C·CO<sub>2</sub>H, Z = CH) has been obtained as follows from benzo[b]thiophene derivatives: (a) from 2-CHO, 3-SeMe by successive treatment with BrCH<sub>2</sub>CO<sub>2</sub>H and Ac<sub>2</sub>O-pyridine; (b) by treatment of 2-CH=CHCO<sub>2</sub>Et, 3-SeMe with bromine, then with pyridine; (c) by cyclization of 2-CHO, 3-SeCH<sub>2</sub>CO<sub>2</sub>Et with NaOEt.<sup>564</sup>

3-Bromomethylbenzo[b]thiophene-2-carbonitrile reacts with KSeCN, and the product **116** (R<sup>1</sup> = CN, X = SeCN, R<sup>2</sup> = H) is cyclized by H<sub>3</sub>PO<sub>3</sub>, to give the selenolactone **134** (X = Se).<sup>565</sup> The sulfur analog **134** (X = S) is formed by cyclizing the 2-CO<sub>2</sub>H, 3-CH<sub>2</sub>SH benzo[b]thiophene derivative with Ac<sub>2</sub>O.



(134)

## P. BENZO[b]THIOPHENE 1,1-DIOXIDES AND 1-OXIDES

### 1. 1,1-Dioxides

Much of the recent work on 1,1-dioxides, apart from that on cycloaddition reactions (Section IIIA,3), has been of a routine nature.

<sup>561</sup> V. P. Litvinov, Ya. L. Gol'dfarb, and V. Yu. Mortikov, *Khim. Geterotsikl. Soedin.*, 905 (1979).

<sup>562</sup> A. Tadino, L. Christiaens, M. Renson, and P. Cagniant, *Bull. Soc. Chim. Belg.* **81**, 595 (1972).

<sup>563</sup> A. Tadino, L. Christiaens, and M. Renson, *Bull. Soc. R. Sci. Liege* **42**, 495 (1973).

<sup>564</sup> E. Iteke, L. Christiaens, and M. Renson, *Bull. Soc. Chim. Fr.*, 4767 (1972).

<sup>565</sup> L. Christiaens and M. Renson, *Tetrahedron* **28**, 5405 (1972).

Flash vapor-phase pyrolysis of benzo[*b*]thiophene 1,1-dioxide gives benzothiete (**60**; X = Y = H) (45%).<sup>566</sup> Other significant reactions have been mentioned in the appropriate Sections.

## 2. 1-Oxides

These have attracted a good deal of attention and have generally been obtained by oxidation of a 2- or 3-substituted benzo[*b*]thiophene with *t*-butyl hypochlorite in MeOH or *t*-BuOH or with *p*-nitroperoxybenzoic acid.<sup>567-570</sup> Because *t*-butyl hypochlorite can also act as a chlorinating agent, the initially formed 1-oxide, particularly with benzo[*b*]thiophene itself, can undergo addition and substitution at the 2,3-bond. The kinetics of the oxidation of a series of 3-substituted benzo[*b*]thiophenes with peroxybenzoic acid have been studied. The rate constants for the first oxidation step (to S = O) and for the second step (to SO<sub>2</sub>) have been correlated with the  $\sigma_p^+$  and  $\sigma_p^-$  constants, respectively.<sup>571</sup>

1-Oxides may also be prepared by cyclization reactions. The alkynes, PhC≡CX, react with SbF<sub>5</sub>-SO<sub>2</sub>-benzene, to give 2-chloro- or 2-bromo-3-phenylbenzo[*b*]thiophene 1-oxide (X = Cl or Br),<sup>572</sup> or with SOCl<sub>2</sub>-AlCl<sub>3</sub>, to give the 1-oxide of 3-chlorobenzo[*b*]thiophene-2-carboxylic acid (or ester or amide) (X = CO<sub>2</sub>H, CO<sub>2</sub>Me, or CONH<sub>2</sub>).<sup>573</sup> More conventionally, the base-catalyzed cyclization of the sulfoxide of *o*-(benzylthio)benzonitrile gives 3-amino-2-phenylbenzo[*b*]thiophene 1-oxide.<sup>388</sup>

Benzo[*b*]thiophene 1-oxides are readily reduced to the corresponding benzo[*b*]thiophene (e.g., with HCl, Zn-AcOH, H<sub>2</sub>/Pd, or H<sub>2</sub>/CoO-MoO<sub>3</sub>-Al<sub>2</sub>O<sub>3</sub>).<sup>573,574</sup>

(-)-2,3-Dihydrobenzo[*b*]thiophene 1-oxide (**135**, X = lone pair) has been obtained elegantly by conversion of the racemate into the (±)-sulfoximide (**135**; X = NH) with hydrazoic acid, resolution of the sulfoximide, and recovery from optically pure **135** (X = NH) with NO<sub>2</sub><sup>+</sup>PF<sub>6</sub><sup>-</sup>.<sup>575</sup> 1-Oxides

<sup>566</sup> W. M. J. van Tilborg and R. Plomp, *Recl. Trav. Chim. Pays-Bas* **96**, 282 (1977).

<sup>567</sup> P. Geneste, J. Grimaud, J.-L. Olivé, and S. N. Ung, *Bull. Soc. Chim. Fr.*, 271 (1977).

<sup>568</sup> P. Geneste, J.-L. Olivé, and S. N. Ung, *J. Heterocycl. Chem.* **14**, 953 (1977).

<sup>569</sup> P. Geneste, J.-L. Olivé, and S. N. Ung, *J. Heterocycl. Chem.* **14**, 449 (1977).

<sup>570</sup> P. Geneste, J. Grimaud, J.-L. Olivé, and S. N. Ung, *Tetrahedron Lett.*, 2345 (1975).

<sup>571</sup> N. Kucharczyk and V. Horák, *Collect. Czech. Chem. Commun.* **34**, 2417 (1969).

<sup>572</sup> S. I. Miller and J. I. Dickstein, *Acc. Chem. Res.* **9**, 358 (1976).

<sup>573</sup> J. Schmitt, M. Suquet, P. Comoy, T. Clim, and G. Callet, *Bull. Soc. Chim. Fr.*, 4575 (1968).

<sup>574</sup> P. Geneste, M. Bonnet, C. Frouin, and D. Levaché, *J. Catal.* **61**, 277 (1980).

<sup>575</sup> F. G. Yamagishi, D. R. Rayner, E. T. Zwicker, and D. J. Cram, *J. Am. Chem. Soc.* **95**, 1916 (1973).

may be converted into the corresponding  $\text{S}^+\text{Me}$  compounds by successive treatment with  $\text{Me}_3\text{O}^+\text{BF}_4^-$  and  $\text{MeMgBr}$ ; for 2,3-dihydro-2-methylbenzo[*b*]thiophene 1-oxide, this conversion takes place with inversion of configuration.<sup>576</sup>



(135)

## V. Metallation of Benzo[*b*]thiophenes

The recognition that a 3-bromobenzo[*b*]thiophene will undergo selective metal-halogen exchange with *n*-butyllithium at low temperatures has proved a major advance in benzo[*b*]thiophene chemistry. Coupled with the long-established fact that benzo[*b*]thiophenes are normally metallated in the 2-position, methods are now available for preparing a wide range of 2,3-disubstituted derivatives. In the simplest example, a 3-bromobenzo[*b*]thiophene containing an unreactive 2-substituent (e.g., Me, SMe, Ph) can be converted directly into the corresponding 3-CO<sub>2</sub>H, 3-CHO, or 3-Me compound<sup>198,199</sup>; a "reactive" 2-substituent such as 2-CHO can be protected as the acetal prior to functionalization of the 3-position.<sup>510</sup> Likewise, a 3-carboxaldehyde can be protected, then lithiated conventionally in the 2-position.<sup>243,510,577</sup> The last two methods have provided a wide range of 2,3-dicarbonyl-containing derivatives. 2,3-Dibromobenzo[*b*]thiophene can be selectively lithiated in the 2-position; then the resulting 2-functionalized 3-bromo derivative can be lithiated again.<sup>332,510,578</sup> Conversely, a 3-bromobenzo[*b*]thiophene can be functionalized in the 3-position, then remetallated in the 2-position. For example, 2-CHO, 3-SeH and 3-CHO, 2-SeH can both be prepared in one-pot reactions from 3-bromobenzo[*b*]thiophene by varying the order of addition of the reagents.<sup>579</sup> Like the 2,3-dibromo compound, the 2,3-dichloro compound is selectively metallated in the 2-position; treatment of the resulting lithio derivative with acid provides a convenient route to 3-chlorobenzo[*b*]thiophene.<sup>243</sup> In contrast, 3-bromo-2-chlorobenzo[*b*]thiophene is first metallated in the 3-position.<sup>243</sup>

<sup>576</sup> K. K. Anderson, R. L. Caret, and I. Karup-Nielsen, *J. Am. Chem. Soc.* **96**, 8026 (1974).

<sup>577</sup> G. Doré, M. Bonhomme, and M. Robba, *Tetrahedron*, **28**, 3277 (1972).

<sup>578</sup> M. G. Reinecke, J. G. Newsom, and K. A. Almqvist, *Synthesis*, 327 (1980).

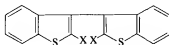
<sup>579</sup> Ya. L. Gol'dfarb, V. P. Litvinov, and V. Yu. Mortikov, *Khim. Geterotsikl. Soedin.*, 898 (1979).

The decomposition of 3-benzo[*b*]thienyllithium into ring-opened products has been discussed in Section III,D.

A mixture of 2- and 3-alkylbenzo[*b*]thiophenes may be separated by treating it with BuLi-CO<sub>2</sub>. The 2-alkyl compound is unaffected and can be removed; the 3-alkyl isomer gives the 2-carboxylic acid, which can then be decarboxylated.<sup>74</sup>

Hexachlorobenzo[*b*]thiophene undergoes metal-halogen exchange; first in the 2-position, then in the 6-position.<sup>342</sup> When benzo[*b*]thiophene is lithiated in the presence of *N,N,N',N'*-tetramethylethylenediamine, under conditions which lead to 2,5-dilithiation in thiophene, some 2,7-dimetallated derivative (12%) is formed.<sup>580</sup>

Specifically deuterated or tritiated benzo[*b*]thiophenes are conveniently obtained from the corresponding bromo compound by treatment of the lithio or magnesio derivative with D<sub>2</sub>O or T<sub>2</sub>O, respectively.<sup>88,333,581</sup> Reduction of 3-bromobenzo[*b*]thiophene with NaBD<sub>4</sub>-PdCl<sub>2</sub> gives the 3-D compound.<sup>582</sup>



(136)



(137)



(138)

BT = 2,3-benzo[*b*]thienophenylene

Unusual polycyclic systems are available via lithiated benzo[*b*]thiophenes. 3,3'-Di(benzo[*b*]thienyl) (136; X = H) is converted into the 2,2'-dialdehyde (136; X = CHO), which reacts with PhCH<sub>2</sub>NH<sub>2</sub>-Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, to give the pentacyclic compound 137.<sup>583</sup> The dilithio compound 136 (X = Li) dimerizes in the presence of CuCl<sub>2</sub>, to give 138 (X = BT).<sup>584</sup> 3-Benzo[*b*]thienyllithium (1 mol) reacts with quinoxaline (1 mol), to give 2-(3-benzo[*b*]thienyl)-

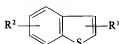
<sup>580</sup> D. J. Chadwick and C. Willbe, *J. C. S. Perkin I*, 887 (1977).

<sup>581</sup> T. R. Bosin and R. B. Rogers, *J. Labelled Compd.* **9**, 395 (1973).

<sup>582</sup> T. R. Bosin, M. G. Raymond, and A. R. Buckpitt, *Tetrahedron Lett.*, 4699 (1973).

<sup>583</sup> H. Wynberg and M. Cabell, *J. Org. Chem.* **38**, 2814 (1973).

<sup>584</sup> T. Kauffmann, B. Greving, J. König, A. Mitscher, and A. Woltermann, *Angew. Chem., Int. Ed. Engl.* **14**, 713 (1975).

TABLE IV  
 SOME BENZO[b]THIOPHENES PREPARED FROM THE 2- OR 3-LITHIO DERIVATIVE


R <sup>1</sup>	R <sup>2</sup>	Reagent(s)	Yield (%)	Ref.
2-Cl	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> Cl	84	243
2-F	H	N <sub>2</sub> F <sub>2</sub>	20	586
2-CHO	3-Piperidino	DMF	35	346
2-CH <sub>2</sub> CH <sub>2</sub> OH	H	Ethylene oxide	58	229
2-OH (oxo tautomer)	3-Me	(a) <i>n</i> -Butyl borate; (b) H <sub>2</sub> O <sub>2</sub>	54	254
2- <i>O</i> - <i>t</i> -Bu	H	(a) MgBr <sub>2</sub> ; (b) PhCO <sub>2</sub> <i>O</i> - <i>t</i> -Bu	79	267
2- or 3-SeH	3- or 2-CHO	Se	21, 25	579
3-SeMe	H	Me <sub>2</sub> Se <sub>2</sub>	80	579
2-SMe	H	Me <sub>2</sub> S <sub>2</sub>	65	347
2-S(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Et	H	(a) S; (b) Br(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Et	90	556
3-N <sub>3</sub>	H	(a) <i>p</i> -Me C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> N <sub>3</sub> ; (b) Na <sub>4</sub> P <sub>2</sub> O <sub>7</sub>	83	367
2-CH <sub>2</sub> Ph	H	PhCH <sub>2</sub> Cl	27	509
3-(3-Benzo[ <i>b</i> ]thienylthio)	H	SCl <sub>2</sub>	47	348
3-(3-Benzo[ <i>b</i> ]thienyl)	H	CuCl <sub>2</sub>	72	583
3-CO·CONMe <sub>2</sub>	4-OMe	Me <sub>2</sub> NCO·CONMe <sub>2</sub>	54	463
3-CH <sub>2</sub> CONMe <sub>2</sub>	4-OCH <sub>2</sub> Ph	BrCH <sub>2</sub> CONMe <sub>2</sub>	63	463
2(C <sub>6</sub> H <sub>4</sub> ·NO <sub>2</sub> - <i>o</i> )	H	<i>o</i> -Fluoronitrobenzene	58	368
3-CH(OH)·CCl <sub>3</sub>	H	CCl <sub>3</sub> CHO	90	549
2-CPh=C(CN) <sub>2</sub>	H	(a) PhCN; (b) CH <sub>2</sub> (CN) <sub>2</sub>	90	587
2-(4,6-Dichloro- <i>s</i> -triazin-2-yl)	H	2,4,6-Trichloro- <i>s</i> -triazine	?	588
2—P< (A phosphorane)	H	>P< (A phosphonium salt)	82	589

quinoxaline, the free thiophene position is then metallated, and the resulting lithio derivative is dimerized in the presence of CuF<sub>2</sub>, to give **138** (X = 2,3-quinoxalinylene).<sup>585</sup>

Table IV, which should be regarded as a supplement to Table XVII in Ref. 2, lists some newer transformations involving lithiated benzo[*b*]-thiophenes.<sup>229,243,254,267,346–348,367,368,463,509,549,556,579,583,586–589</sup> It is not an exhaustive catalog of reactions; it merely illustrates the scope of the metallation reaction.

<sup>585</sup> T. Kauffmann and R. Otter, *Angew. Chem., Int. Ed. Engl.* **15**, 500 (1976).

<sup>586</sup> J. Bensoam and F. Mathey, *Tetrahedron Lett.*, 2797 (1977).

<sup>587</sup> E. Campaigne, D. Mais, and E. M. Yokley, *Synth. Commun.* **4**, 379 (1974).

<sup>588</sup> J. K. Chakrabarti, R. W. Goulding, and A. Todd, *J. C. S. Perkin I*, 2499 (1973).

<sup>589</sup> E. M. Richards and J. C. Tebb, *J. Chem. Soc. C*, 1425 (1970).

## VI. Hydrodesulfurization of Benzo[*b*]thiophenes

The use of hydrodesulfurization by Raney nickel as a means of determining structures of benzo[*b*]thiophenes has been largely superseded by spectroscopic methods.

Acylenamines,  $\text{PhC}(\text{NHET})=\text{CHCOR}$  ( $\text{R} = \text{Et}$ , *t*-Bu, or H), of known stereochemistry have been obtained in high yield by hydrodesulfurization of 2-acyl-3-ethylaminobenzo[*b*]thiophenes.<sup>583</sup> An SMe substituent on the benzo[*b*]thiophene nucleus can be removed without rupture of the thiophene ring by using Raney nickel in acetone.<sup>599</sup>

In view of the increasing demand for fuels containing the minimum amount of sulfur compounds, the catalytic hydrodesulfurization of benzo[*b*]thiophene (usually in the presence of  $\text{CoO}-\text{MoO}_3-\text{Al}_2\text{O}_3$ ) is an economically important reaction, and its mechanism has been studied in considerable detail. The overall conversion of benzo[*b*]thiophene into ethylbenzene may take place by initial hydrogenation of the thiophene double bond, followed by removal of sulfur (route A) or by hydrodesulfurization and subsequent hydrogenation of the resulting styrene (route B). However, because the processes that take place depend on many factors (e.g., temperature, hydrogen pressure, type of catalyst, operating conditions), the results which have been obtained are conflicting and confusing. Route B<sup>590-596</sup> is generally favored over route A,<sup>597,598</sup> but the reaction may involve a combination of the two.<sup>599</sup> In hydrodesulfurization reactions, 1-oxides are initially deoxygenated; 1,1-dioxides are successively hydrogenated, deoxygenated, and desulfurized.<sup>598</sup> The kinetics of the hydrodesulfurization of benzo[*b*]thiophene over  $\text{CoO}$  (or  $\text{NiO}$ )- $\text{MoO}_3-\text{Al}_2\text{O}_3$  have been studied.<sup>600-602</sup> The role of the hydrodesulfurization catalyst has been

<sup>590</sup> R. Bartsch and C. Tanielian, *J. Catal.* **35**, 353 (1974).

<sup>591</sup> V. H. J. de Beer, J. G. J. Dahlmans, and J. G. M. Smeets, *J. Catal.* **42**, 467 (1976).

<sup>592</sup> E. Furimsky and C. H. Amberg, *Can. J. Chem.* **54**, 1507 (1976).

<sup>593</sup> L. D. Rollmann, *J. Catal.* **46**, 243 (1977).

<sup>594</sup> D. R. Kilanowski, H. Teeuwen, V. H. J. de Beer, B. C. Gates, G. C. A. Schuit, and H. Kwart, *J. Catal.* **55**, 129 (1978).

<sup>595</sup> N. K. Nag, A. V. Sapre, D. H. Broderick, and B. C. Gates, *J. Catal.* **57**, 509 (1979).

<sup>596</sup> R. Bartsch and C. Tanielian, *J. Catal.* **50**, 35 (1977).

<sup>597</sup> E. N. Givens and P. B. Venuto, *Am. Chem. Soc., Div. Fuel Chem., Prepr.* **14** (Pt. 2), 135 (1970).

<sup>598</sup> P. Geneste, P. Amblard, M. Bonnet, and P. Graffin, *J. Catal.* **61**, 115 (1980).

<sup>599</sup> F. P. Daly, *J. Catal.* **51**, 221 (1978).

<sup>600</sup> S. Morooka and C. E. Hamrin, *Chem. Eng. Sci.* **34**, 521 (1979).

<sup>601</sup> D. R. Kilanowski and B. C. Gates, *J. Catal.* **62**, 70 (1980).

<sup>602</sup> M. Sugioaka, K. Aomura, and I. G. Dalla Lana, *Hokkaido Daigaku Kogakubu Kenkyu Hokoku*, 91 (1978) [*CA* **91**, 38582 (1979)].

much discussed. Previously it was believed that adsorption involved bonding of the sulfur atom of the reactant with Mo ions at an anion vacancy on the catalyst surface ("one-point adsorption"). Alternatively, it is now suggested that the double bond of the thiophene ring interacts with a Mo cation, and that the sulfur atom of the reactant interacts with a sulfur ion on the catalyst surface ("multipoint adsorption").<sup>595,603</sup>

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I am indebted to Dr. P. G. Nelson for advice on theoretical aspects of the subject. I greatly appreciate the tolerance which my research students have displayed, at least outwardly, during my prolonged absence from the laboratory.

<sup>603</sup> H. Kwart, G. C. A. Schuit, and B. C. Gates, *J. Catal.*, **61**, 128 (1980).



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# Furoxans and Benzofuroxans

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## I. Introduction: The Literature on Furoxans

The furoxan (furazan oxide, 1,2,5-oxadiazole-2-oxide) ring system has been the subject of much debate and controversy since the first (unrecognized) preparation of a compound of this type in the 1850s<sup>1</sup> until almost the present day. The history of the structure problem is briefly outlined in the following section; it is sufficient here to state that proton magnetic resonance spectroscopy resolved the benzofuroxan question at the beginning of the 1960s, while X-ray crystallography cleared up all doubts that might have remained concerning the unfused series in the latter half of that decade. However, as

<sup>1</sup> A. Kekulé, *Justus Liebigs Ann. Chem.* **101**, 200 (1857); **105**, 279 (1858).

will become apparent, there are still many unsolved problems in this area of chemistry.

The "furoxan" nomenclature is not used either by *Chemical Abstracts* or the I.U.P.A.C., which are unwilling to reserve a special name for a class of compounds that are (now known to be) the *N*-oxides of another class. These are the furazans (1,2,5-oxadiazoles), which are given the benefit of a special trivial name approved (except by *Chemical Abstracts*) for use in fusion nomenclature.<sup>2</sup> It is nevertheless convenient to retain the word "furoxan" as a useful handle for a large and well-defined group of substances, to avoid both the otiose repetition of "furazan oxide," and the formation of names containing clumsy conjunctions of noun elements. In *Chemical Abstracts* (9th Cumulative Index), furazans and benzofurazans are listed as such, but other fused furazans appear as 1,2,5-oxadiazoles; the corresponding furoxans are entered as derivatives of these. A search using the *Abstracts* as data-base source needs to take all these possibilities into account. The older literature (pre-1950) also requires careful reading, since four different ring systems, and one acyclic formulation, were used at one time or another to represent the furoxans (see Section II).

Three major reviews<sup>3-5</sup> covering the area were published during the confused period before the structural clarification referred to above. Three others,<sup>6-8</sup> concerned exclusively with the benzofuroxans, have appeared more recently; the last two of these are devoted to a single reaction (see Section V,C,3) that has attracted a considerable amount of attention in recent years. A brief review of a more general nature<sup>9</sup> and some still briefer entries in monographs of heterocyclic<sup>10</sup> and general organic<sup>11</sup> chemistry complete the list of those articles on furoxans which have come to the authors' attention.

The present review covers the period from 1960 until the middle of 1980. While earlier work will, in general, be dealt with by reference to the reviews<sup>3-5</sup> mentioned above, certain areas that require further clarification will be discussed with reference also to the older literature. The benzofuroxans and

<sup>2</sup> I.U.P.A.C. Rule B.2.11; see A. D. McNaught, *Adv. Heterocycl. Chem.* **20**, 287 (1976).

<sup>3</sup> J. V. R. Kaufman and J. P. Picard, *Chem. Rev.* **59**, 429 (1959).

<sup>4</sup> J. H. Boyer, *Heterocycl. Compd.* **7**, 462 (1961).

<sup>5</sup> L. C. Behr, *Chem. Heterocycl. Compd.* **17**, 295 (1962).

<sup>6</sup> A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.* **10**, 1 (1969).

<sup>7</sup> K. Ley and F. Seng, *Synthesis*, 415 (1975).

<sup>8</sup> M. J. Haddadin and C. H. Issidorides, *Heterocycles* **4**, 767 (1976).

<sup>9</sup> K. L. Stuart, *Heterocycles* **3**, 651 (1975).

<sup>10</sup> R. M. Scrowston, *Heterocycl. Compd., Ser. One* **4**, 293 (1975).

<sup>11</sup> M. M. Campbell, in "Comprehensive Organic Chemistry," (P. G. Sammers, ed.) Vol. 4, p. 1029. Pergamon, Oxford, 1979.

other ring-fused analogs, which were reviewed in this series<sup>6</sup> in 1969, are brought up to date from that time.

## II. Structure

### A. HISTORY

We shall not attempt a full account of the extended controversy over the structure of furoxans. Kaufman and Picard<sup>3</sup> have summarized the early history of the problem and in most respects have given an adequate picture. Boyer<sup>4</sup> and Behr<sup>5</sup> (the latter particularly for the fulminic acid oligomers) also reviewed the debate, and an account also appears in Beilstein's *Handbuch*.<sup>12</sup> What follows here is a brief summary of the development of the major theories, from the early times until the final proof of the Wieland-Werner structure (1), some 60 years after it was first suggested.

The earliest furoxans were produced from metal fulminates. The dibromo compound,  $C_2Br_2N_2O_2$ , formed by the action of bromine on mercury fulminate,<sup>1</sup> was for some time believed to be dibromonitroacetonitrile, until chemical investigation<sup>13</sup> and an authentic synthesis<sup>14</sup> forced that notion to be abandoned. In the meantime, other ways were found of producing furoxans that provided more insight into their structures. Syntheses of furoxans from 1,2-dioximes (glyoximes) by oxidation<sup>15</sup> and by the action of oxides of nitrogen on certain olefins<sup>16,17</sup> (see Sections IV,B and C) showed the need for a more symmetrical formula, and the dioxadiazine, or glyoxime peroxide, structure (2) was put forward.<sup>15</sup> Wieland<sup>18,19</sup> first proposed the oxadiazole *N*-oxide formula (1) (although he later rejected it for a while in favor of the bicyclic structure 3, which never gained wide currency), and Werner independently put forward the same idea.<sup>20</sup> Another bicyclic structure (4) enjoyed brief popularity as it was capable of explaining the lack of isomerism in the benzofuroxans (see below).<sup>21</sup> It fell out of use for

<sup>12</sup> "Beilstein's Handbuch der Organischen Chemie," Hauptwerk, 4th ed., Vol. 27, p. 562. Springer-Verlag, Berlin and New York, 1937.

<sup>13</sup> A. F. Holleman, *Ber. Dtsch. Chem. Ges.* **26**, 1403 (1893).

<sup>14</sup> W. Steinkopf and L. Bohrmann, *Ber. Dtsch. Chem. Ges.* **41**, 1044 (1908).

<sup>15</sup> R. Koreff, *Ber. Dtsch. Chem. Ges.* **19**, 176 (1886).

<sup>16</sup> P. Tönnies, *Ber. Dtsch. Chem. Ges.* **13**, 1845 (1880).

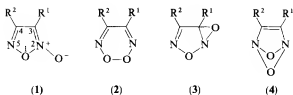
<sup>17</sup> A. Angeli, *Ber. Dtsch. Chem. Ges.* **26**, 593 (1893).

<sup>18</sup> H. Wieland, *Justus Liebigs Ann. Chem.* **329**, 225 (1903).

<sup>19</sup> H. Wieland and L. Semper, *Justus Liebigs Ann. Chem.* **358**, 36 (1907).

<sup>20</sup> A. Werner, "Lehrbuch der Stereochemie," p. 260. Fischer, Jena, 1904.

<sup>21</sup> A. G. Green and F. M. Rowe, *J. Chem. Soc.* **103**, 897 (1913).



the unfused series when isomerism was demonstrated for cases in which  $R^1$  and  $R^2$  are different.

The main objection to the peroxide structure (2) was that it was inconsistent with the chemical properties of furoxans—in particular, their stability, and their oxidizing power, which is not pronounced. Both of Wieland's formulas (1 and 3) require that isomeric substances can exist when  $R^1$  and  $R^2$  are not the same, but at the time of his proposal (1903) isomerism had not been established. Although Wieland later believed that he had isolated two isomers of monophenylfuroxan (see Section VI), the first sound evidence came only in 1925, when Meisenheimer *et al.*<sup>22</sup> showed that different isomers could be produced from different stereoisomers of *p*-methoxybenzil dioxime (see Section VII,A). Shortly afterward, isomers, and their interconversion, were found in the aryl-alkyl series.<sup>23-25</sup> This evidence led Beilstein's *Handbuch*<sup>12</sup> to recommend the furoxan structure (1). However, in certain quarters it was felt that some pairs of isomers showed differences in their chemical properties that were too wide to be explained by simple positional isomerism. The chief protagonist for this view was Ponzio, whose prolific output dominated (and, in this respect, confused) the furoxan literature in the 1920s and 1930s. He held that most cases of isomerism were not simply positional, but that different ring systems were involved. Several criteria for distinction between the series were applied; so far as the aryl methyl isomers were concerned, the principal ones were that compounds which could be deoxygenated by phosphorus pentachloride (see Section V,D,3), and underwent the Angeli rearrangement (Section V,C,1), were furoxans (1), while those which failed to show these reactions were dioxadiazines (2). Cases for which the dichotomy was not so clear-cut (as with Meisenheimer's diaryl isomers<sup>22</sup>) he was reluctant to commit to either structure.<sup>26</sup> It is not always clear exactly what Ponzio intended to convey: sometimes he used the term "peroxide" to refer specifically to structure 2, but on other occasions the term was a non-committal expression, to embrace both possibilities 1 and 2; at these times, when he meant 2, he used the name "dioxadiazine."

<sup>22</sup> J. Meisenheimer, H. Lange, and W. Lamparter, *Justus Liebigs Ann. Chem.* **444**, 94 (1925).

<sup>23</sup> G. Ponzio, *Gazz. Chim. Ital.* **58**, 329 (1928), *Ber. Dtsch. Chem. Ges.*, **61**, 1316 (1928).

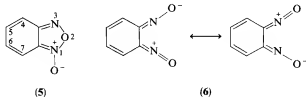
<sup>24</sup> G. Ponzio and G. Carta-Satta, *Gazz. Chim. Ital.* **60**, 150 (1930).

<sup>25</sup> G. Ponzio, *Gazz. Chim. Ital.* **59**, 713 (1929).

<sup>26</sup> G. Ponzio, *Gazz. Chim. Ital.* **60**, 49 (1930).

Ponzio's position at this time (the late 1920s) was open to the objection—very much the reverse of that which Wieland faced in 1904—that, if two different ring systems exist, then isomeric compounds should be capable of isolation even when the substituents  $R^1$  and  $R^2$  are the same. To counter this, he relied heavily on the apparent existence of two isomers of dibenzoylfuroxan<sup>27,28</sup> (Section IV,A,2). However, these could not be interconverted (and much later<sup>29</sup> it was shown that they were not isomers after all), while the aryl-alkyl isomers could.<sup>25</sup> Nevertheless, the position remained unclarified for many years, and in 1959 Kaufman and Picard<sup>3</sup> accepted, with reservations, the dioxadiazine formula for some of the isomers (see Section VII,A). The later reviewers (Boyer<sup>4</sup> and Behr<sup>5</sup>) correctly assign furoxan structures throughout. This view seems also to have been accepted by Ponzio at the end; although he never publicly retracted his support for the dioxadiazine formulas, a number of compounds that are described as such in his publications are labeled as furoxans in his sample collection which is held in Turin. Somewhat earlier, in reworking the question of the phenylfuroxan isomers (Section VI), he considered a *cis*- or *trans*- $\alpha,\beta$ -dinitrostyrene structure for one of them, in order to avoid the apparent oxygen migration from one nitrogen atom to the other in the interconversion of furoxans [ $1$  ( $R^1 = H$ ,  $R^2 = Ph$ )  $\rightarrow$   $1$  ( $R^1 = Ph$ ,  $R^2 = H$ )], which he considered was improbable.<sup>30</sup> But this notion was untenable and quickly discarded. It was only in the mid-1960s that NMR<sup>31</sup> and X-ray<sup>32</sup> evidence was obtained for the identity of both isomers of some pairs as furoxans (**1**), but by that time the general consensus was that this was the case.

The benzofuroxans and naphthofuroxans presented an apparently different problem, because the isomerism that might have been expected by analogy with the monocyclic series was not found. Although by the time of Beilstein's Second Supplement (1929) the furoxan structure (**5**) was considered the most likely, another symmetrical formula, " $\psi$ -(pseudo-) *o*-dinitrosoben-



<sup>27</sup> A. F. Holleman, *Ber., Dtsch. Chem. Ges.* **20**, 3359 (1887); **21**, 2835 (1888).

<sup>28</sup> G. Ponzio, *Gazz. Chim. Ital.* **62**, 633 (1932).

<sup>29</sup> J. H. Boyer and M. S. Chang, *J. Am. Chem. Soc.* **82**, 2220 (1960).

<sup>30</sup> G. Ponzio, *Gazz. Chim. Ital.* **66**, 134 (1936).

<sup>31</sup> F. B. Mallory and A. Cammarata, *J. Am. Chem. Soc.* **88**, 61 (1966).

<sup>32</sup> M. Calleri, G. Ferraris, and D. Viterbo, *Tetrahedron Lett.*, 4549 (1967).

zene" (6), was put forward in 1955 by Boyer, whose review<sup>4</sup> is to a large extent colored by this. But in 1961, incontrovertible evidence for a rapidly exchanging system<sup>33</sup> led to a reinstatement of the benzofuroxan formula (5), with the interconversion of isomers which had long previously been suggested by Hammick *et al.*<sup>34</sup> X-Ray crystallography almost immediately confirmed this as correct.<sup>35</sup>

## B. THEORETICAL CALCULATIONS

Häfelinger<sup>36</sup> applied the Hückel molecular orbital (HMO) method to a wide variety of compounds containing N—O bonds, including four furoxans, for which the bond lengths were known from X-ray structure determinations. Comparison of N—O calculated bond orders and experimental bond lengths, using two different sets of parameters to calculate the bond orders, gave fair linear correlations, particularly when the resonance integrals for N=O and N<sup>+</sup>—O<sup>-</sup> were assigned increased values. However, even with this correction, the furoxan points were among the most reluctant to approach the correlation line, the exocyclic N—O bond being shorter and the endocyclic N(2)—O(1) bond longer than the calculations predicted.

Sosa and Paoloni<sup>37</sup> used antisymmetrical molecular orbital calculations by the Pariser-Parr-Pople (PPP) procedure for benzofuroxan and its 5-chloro, methoxy, amino, and dimethylamino derivatives. They found fair agreement between theory and experiment as regards the ultraviolet spectra, but the method was less satisfactory at predicting the equilibrium constants between 1- and 3-oxide isomers of the 5-chloro and 5-methoxy compounds. Uematsu and Akahori<sup>38</sup> found that the equilibria of the 5-halobenzofuroxans were predicted satisfactorily by a HMO method. On the (questionable) assumption that the transition state is approximately described by the  $\psi$ -*o*-dinitrosobenzene structure (6), reasonable activation energies (80 kJ mol<sup>-1</sup>; cf. Section V,B) were found for the equilibration. The reaction has also been the subject of CNDO/2 calculations, made with a view to locating minima (if any) on the energy profile.<sup>39</sup> A nonplanar reaction pathway, as predicted from orbital symmetry considerations,<sup>40</sup> was here assumed.

<sup>33</sup> A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.* **10**, 8 (1969).

<sup>34</sup> D. L. Hammick, W. A. M. Edwardes, and E. R. Steiner, *J. Chem. Soc.*, 3308 (1931).

<sup>35</sup> R. Hulme, *Chem. Ind. (London)*, 42 (1962); D. Britton and W. E. Noland, *Ibid.*, 563.

<sup>36</sup> G. Häfelinger, *Chem. Ber.* **103**, 3370 (1970).

<sup>37</sup> R. Sosa and L. Paoloni, *Tetrahedron* **25**, 4197 (1969).

<sup>38</sup> S. Uematsu and Y. Akahori, *Chem. Pharm. Bull.* **26**, 25 (1978).

<sup>39</sup> G. Calzaferri, R. Gleiter, K.-H. Knauer, H.-D. Martin, and E. Schmidt, *Angew. Chem. Int. Ed. Engl.* **13**, 86 (1974).

<sup>40</sup> R. Hoffmann, R. Gleiter, and F. B. Mallory, *J. Am. Chem. Soc.* **92**, 1460 (1970).



This has been a somewhat neglected area of furoxan research, and no doubt more refined techniques will in the future yield more satisfactory results.

### C. X-RAY DIFFRACTION STUDIES

Many furoxan structures have been determined by crystallographic methods, and as a result the dimensions of the heterocyclic ring are known in a wide variety of fused and substituted examples. The earliest to be studied were the benzofuroxans, for which the rather rough results that were obtained confirmed their bicyclic structures.<sup>35</sup> Of the many subsequent determinations, a considerable number have been of pairs of isomers with a methyl group as one of the substituents. Table I lists the compounds which have been studied.<sup>41-63</sup>

The available data allow the following general conclusions. The ring bond lengths and angles do not vary very much; such trends as seem significant

<sup>41</sup> M. Calleri, G. Ferraris, and D. Viterbo, *Acta Crystallogr.* **25B**, 1133 (1969).

<sup>42</sup> M. Calleri, G. Ferraris, and D. Viterbo, *Acta Crystallogr.* **25B**, 1126 (1969).

<sup>43</sup> M. Calleri, G. Chiari, A. Chiesi Villa, A. Gaetani Manfredotti, C. Guastini, and D. Viterbo, *Acta Crystallogr.* **31B**, 2384 (1975).

<sup>44</sup> A. Chiesi Villa, C. Guastini, M. Calleri, and G. Chiari, *Cryst. Struct. Commun.* **3**, 265 (1974).

<sup>45</sup> M. Calleri, D. Viterbo, A. Gaetani Manfredotti, and C. Guastini, *Cryst. Struct. Commun.* **3**, 269 (1974).

<sup>46</sup> M. Calleri, G. Chiari, G. Germain, and D. Viterbo, *Acta Crystallogr.* **29B**, 1618 (1973).

<sup>47</sup> G. Germain and D. Viterbo, *Cryst. Struct. Commun.* **1**, 411 (1972).

<sup>48</sup> M. Calleri, G. Chiari, and D. Viterbo, *Cryst. Struct. Commun.* **1**, 407 (1972).

<sup>49</sup> M. Calleri, G. Chiari, A. Chiesi Villa, A. Gaetani Manfredotti, C. Guastini, and D. Viterbo, *Acta Crystallogr.* **32B**, 1032 (1976).

<sup>50</sup> M. Calleri, G. Chiari, A. Chiesi Villa, A. Gaetani Manfredotti, C. Guastini, and D. Viterbo, *Acta Crystallogr.* **33B**, 479 (1977).

<sup>51</sup> A. F. Cameron and A. A. Freer, *Acta Crystallogr.* **30B**, 354 (1974).

<sup>52</sup> T. Osawa, Y. Kito, M. Namiki, and K. Tsuji, *Tetrahedron Lett.*, 4399 (1979).

<sup>53</sup> C. Glidewell, H. D. Holden, and D. C. Liles, *J. Chem. Res. (S)*, 357 (1978).

<sup>54</sup> D. Viterbo and G. Ferraris, *J. Chem. Soc. B*, 223 (1970).

<sup>55</sup> A. K. Sillitoe and M. M. Harding, *Acta Crystallogr.* **34B**, 2021 (1978).

<sup>56</sup> A. Battaglia, A. Dondoni, C. Panattoni, G. Bandoli, and D. A. Clemente, *Tetrahedron Lett.*, 2907 (1971).

<sup>57</sup> C. Panattoni, D. A. Clemente, G. Bandoli, A. Battaglia, and A. Dondoni, *J. C. S. Chem. Commun.*, 60 (1970).

<sup>58</sup> M. Calleri, S. A. Chawdhury, and D. Viterbo, *Acta Crystallogr.* **32B**, 2678 (1976).

<sup>59</sup> M. Calleri, L. Bonaccorti, and D. Viterbo, *Acta Crystallogr.* **33B**, 3546 (1977).



<sup>60</sup> M. Calleri and D. Viterbo, *Acta Crystallogr.* **32B**, 2236 (1976).

<sup>61</sup> J. F. Barnes, M. J. Barrow, M. M. Harding, R. M. Paton, P. L. Ashcroft, J. Crosby, and C. J. Joyce, *J. Chem. Res. (S)*, 314; (*M*), 3601 (1979).

<sup>62</sup> M. Calleri, D. Viterbo, A. Chiesi Villa, and C. Guastini, *Cryst. Struct. Commun.* **4**, 13 (1975).

<sup>63</sup> M. Calleri, G. Chiari, and D. Viterbo, *Cryst. Struct. Commun.* **2**, 335 (1973).

TABLE I  
FUROXANS STUDIED BY X-RAY CRYSTALLOGRAPHY

No.	Substituent at position		Ref.	No.	Substituent at position		Ref.
	3	4			3	4	
1	Me	C <sub>6</sub> H <sub>4</sub> Br( <i>p</i> )	41	18	C <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	C <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	56
2	C <sub>6</sub> H <sub>4</sub> Br( <i>p</i> )	Me	42	19*	C <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	C <sub>6</sub> H <sub>4</sub> OMe( <i>p</i> )	57
3	Me	CONH <sub>2</sub>	43	20	—CH <sub>2</sub> CMe <sub>2</sub> CD <sub>2</sub> C(OH)( <i>E</i> )—		58
4	CONH <sub>2</sub>	Me	43	21	—C(OH)( <i>E</i> )CH <sub>2</sub> CMe <sub>2</sub> CH <sub>2</sub> —		59
5	Me	CONMe <sub>2</sub>	44	22	—COCH <sub>2</sub> CMe <sub>2</sub> CH <sub>2</sub> —		60
6	CONMe <sub>2</sub>	Me	45	23	—CH <sub>2</sub> —CH <sub>2</sub> —CH <sub>2</sub> —		61
7	Me	CONHNH <sub>2</sub>	46, 47				
8	CONHNH <sub>2</sub>	Me	46, 48				
9	Me	SO <sub>2</sub> Ph	49				
10	SO <sub>2</sub> Ph	Me	49				
11	Me	NHCOOCHMe <sub>2</sub>	50	24			62
12	NHCOOCHMe <sub>2</sub>	Me	50				
13	Me	NO <sub>2</sub>	51				
14	Me	CH=CH( <i>E</i> )COOH	52				
15	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	NHC <sub>6</sub> H <sub>4</sub> Br( <i>p</i> )	53	25			63
16	COC <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	COC <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	54				
17	Ph	Ph	55				

\* Mixed crystals, containing ~46% of the other isomer.

are noted below. The ring is planar, and the exocyclic oxygen is always within 0.05 Å of this plane. The first 12 compounds of Table I are taken as representative examples of unfused furoxans, and the ranges of their bond lengths and angles are listed in Table II. Noteworthy features are the rather long O(1)—N(2) bond (*a*) and the unusually short N(2)—O(*exo*) bond (*x*). The latter does not show any noticeable further shortening as a result of conjugation with electron-withdrawing substituents at C(3).

TABLE II  
BOND LENGTHS AND ANGLES IN  
COMPOUNDS 1–12 OF TABLE I



Bond	Length (Å)	Bonds	Angle (deg)
<i>a</i>	1.42–1.46	<i>a</i> – <i>b</i>	107–109
<i>b</i>	1.30–1.33	<i>b</i> – <i>c</i>	104–109
<i>c</i>	1.40–1.43	<i>c</i> – <i>d</i>	110–116
<i>d</i>	1.29–1.31	<i>d</i> – <i>e</i>	105–109
<i>e</i>	1.36–1.39	<i>e</i> – <i>a</i>	107–108
<i>x</i>	1.22–1.24	<i>a</i> – <i>x</i>	116–118

Among the fused furoxans are the strained examples, Nos. 23 and 25 of Table I. These show even longer O(1)—N(2) bonds (*a*) than usual (1.49 and 1.50 Å, respectively), which may be a reflection of their tendency to break apart at this bond (see Section V,A). However, this tendency is shown even more noticeably in the benzofuroxans (Table III),<sup>64–71</sup> in which bond *a*, although longer than usual, is shorter than in Nos. 23 and 25. The 4,6-dinitrobenzofuroxan (No. 30) is an interesting case: here the two ring N—O bonds are nearly the same length. In this compound the N(5)—O(1) bond (*e*) also shows a tendency to cleavage (Section V,C,4). Some of the papers

<sup>64</sup> D. Britton and W. E. Noland, *J. Org. Chem.* **27**, 3218 (1962).

<sup>65</sup> D. Britton, G. L. Hardgrove, R. Hegström, and G. V. Nelson, *Acta Crystallogr.* **28B**, 1121 (1972).

<sup>66</sup> R. C. Gehrz and D. Britton, *Acta Crystallogr.* **28B**, 1126 (1972).

<sup>67</sup> D. Britton and W. E. Noland, *Acta Crystallogr.* **28B**, 1116 (1972).

<sup>68</sup> D. Britton, J. Konner, J. Hamer, and L. M. Trefonas, *Acta Crystallogr.* **28B**, 1123 (1972).

<sup>69</sup> C. K. Prout, O. J. R. Hodder, and D. Viterbo, *Acta Crystallogr.* **28B**, 1523 (1972).

<sup>70</sup> M. Calleri, L. Bonaccorti, and D. Viterbo, *Acta Crystallogr.* **33B**, 3685 (1977).

<sup>71</sup> H. H. Cady, A. C. Larson, and D. T. Cromer, *Acta Crystallogr.* **20**, 336 (1966).

TABLE III  
BOND LENGTHS IN SUBSTITUTED BENZOFUROXANS



No.	Substituent at position				Bond lengths (Å)						Ref.
	4	5	6	7	a	b	c	d	e	x	
26 <sup>a</sup>	—	Cl	—	—	1.40	1.46	1.36	1.50	1.23	1.11	64, 65
27	—	I	—	—	1.44	1.33	1.40	1.33	1.38	1.24	66
28	—	Me	—	—	1.45	1.33	1.41	1.33	1.39	1.24	67
29 <sup>b</sup>	—	Cl	Cl	—	1.45	1.33	1.40	1.32	1.38	1.23	68
30	NO <sub>2</sub>	—	NO <sub>2</sub>	—	1.41	1.40	1.40	1.37	1.42	1.22	69
31	—	—	=N—S—N=	—	1.47	1.31	1.42	1.31	1.38	1.23	70
32 <sup>c</sup>	=NO—O—N=	—	=NO—O—N=	—	1.48	1.34	1.42	1.32	1.39	1.23	71

<sup>a</sup> Bond lengths shown are probably considerably in error. The 5-bromo derivative was also studied, but the molecular dimensions depended upon measurements made on No. 28 and are not listed here.

<sup>b</sup> Disordered arrangement of molecules in the unit cell.

<sup>c</sup> Benzotrifuroxan; average bond lengths listed.

which report on substituted benzofuroxans publish only the atomic coordinates; the furoxan bond lengths and angles have been calculated and are listed in Table III.

Benzofuroxans usually crystallize in the tautomeric form which predominates in solution. An exception is the thiadiazolo-fused compound (No. 31 of Table III), where the isomer which is found in the crystal<sup>70</sup> is the minor form in solution.<sup>72</sup>

Besides intramolecular bond lengths and angles, the crystal packing and intermolecular contacts of some of the substituted benzofuroxans have been discussed.<sup>65-68</sup>

Intramolecular hydrogen bonding to the *N*-oxide group is evident in the amide and hydrazide derivatives Nos. 4 and 8 (Table I).<sup>43,46</sup>

### III. Spectroscopic and Other Physical Properties

#### A. INFRARED SPECTRA

The infrared spectra of several furoxan derivatives have been studied in the region 3300–400 cm<sup>-1</sup>. According to N. E. Boyer *et al.*,<sup>73</sup> six or seven absorption bands are particularly useful. Table IV lists these, and their suggested assignments. The bands in the region 1650–1300 are generally strong, and they have been used by many authors for diagnostic purposes. J. H. Boyer *et al.*<sup>74</sup> also reported the spectra of a variety of furoxans and benzofuroxans, drawing attention to their similarity. Soviet authors have also made an infrared study of the ring vibrations.<sup>75</sup>

An infrared investigation of the products from phenylglyoxime and dinitrogen tetroxide<sup>77</sup> requires revision in the light of more recent results on this reaction (Section VI).

Substituent bands have received sporadic attention. The spectra of some bis(arylamino-carbonyl)furoxans<sup>78</sup> and of the two methylfuroxan carboxylic acid isomers<sup>79</sup> show the existence of an intramolecular hydrogen bond

<sup>72</sup> C. J. Creswell and R. K. Harris, *J. Magn. Reson.*, **4**, 99 (1971).

<sup>73</sup> N. E. Boyer, G. M. Czerniak, H. S. Gutowsky, and H. R. Snyder, *J. Am. Chem. Soc.*, **77**, 4238 (1955).

<sup>74</sup> J. H. Boyer, U. Toggweiler, and G. A. Stoner, *J. Am. Chem. Soc.*, **79**, 1748 (1957).

<sup>75</sup> B. E. Zaitsev, Z. V. Todres, and V. A. Pozdyshev, *Khim. Geterotsikl. Soedin.*, 825 (1965) [*CA* **64**, 15705 (1966)].



<sup>76</sup> J. F. Barnes, R. M. Paton, P. L. Ashcroft, R. Bradbury, J. Crosby, C. J. Joyce, D. R. Holmes, and J. A. Milner, *J. C. S. Chem. Commun.*, 113 (1978).

<sup>77</sup> E. Borello and M. Colombo, *Ann. Chim. (Rome)*, **46**, 1158 (1956).

<sup>78</sup> S. P. Parikh, M. R. Patel, and B. N. Mankad, *Indian J. Chem.*, **11**, 198 (1973).

<sup>79</sup> A. Gasco and A. J. Boulton, *J. C. S. Perkin II*, 1613 (1973).

TABLE IV  
 FUOXAN INFRARED ABSORPTION BANDS

$\nu_{\max}$ (cm <sup>-1</sup> )	Assignment	$\nu_{\max}$ (cm <sup>-1</sup> )	Assignment
1625–1600 <sup>a</sup>	C=N <sup>+</sup> —O <sup>-</sup>	1190–1150	
1475–1410		1030–1000 890–840	
1360–1300	N—O	950–900 <sup>b</sup>	

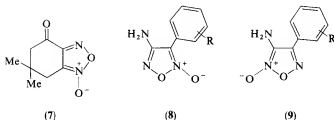
<sup>a</sup> Occurs at higher frequency in strained furoxans.<sup>76</sup><sup>b</sup> In diaryl and diaroyl furoxans and their derivatives.

between the *N*-oxide group and the proton on the CONHAr substituent when it is at the 3-position. The carbonyl stretching frequencies of some cyclic furoxan ketones<sup>80</sup> and also of some other methylfuroxan carboxylic acid derivatives<sup>79</sup> have been reported. The intensities of the symmetrical CH stretching vibration(s) in the spectra of a number of five-membered heterocyclic methyl compounds, including dimethylfuroxan, have been correlated with CNDO/2-calculated charges on the C and H atoms.<sup>81</sup>

## B. ULTRAVIOLET SPECTRA

Although ultraviolet data on furoxans are widespread in the literature, going back to a very early paper of Milone,<sup>82</sup> no systematic work has been performed. Dimethylfuroxan shows a broad band of medium intensity at 258 nm in ethanol,<sup>74,75,83</sup> which is shifted to the red in aprotic solvents.<sup>75</sup> A similar band is present in the spectra of other simple furoxans with chloro, acetyl, and dinitroethyl substituents,<sup>83</sup> and also in bisdialkylaminofuroxans,<sup>84</sup> where the maximum is at somewhat longer wavelengths. Data are also available on isomeric cyclic acylfuroxans, e.g., 7,<sup>80</sup> alkyl-aryl-furoxans,<sup>85</sup> and amino-aryl-furoxans.<sup>86</sup> In the last, hypsochromic and hypochromic effects are seen when the 3-phenyl isomer (8) carries an ortho substituent; these are not observed in the isomeric 4-aryl derivatives (9).<sup>86</sup>

<sup>80</sup> J. Ackrell and A. J. Boulton, *J. C. S. Perkin I*, 351 (1973).<sup>81</sup> N. N. Zatschina, I. F. Tupitsyn, A. I. Belyashova, A. A. Kane, N. S. Kolodina, and G. N. Sudakova, *Khim. Geterotsikl. Soedin.*, 1110 (1977) [*CA* 87, 183818 (1977)].<sup>82</sup> M. Milone, *Gazz. Chim. Ital.* 62, 432 (1932).<sup>83</sup> H. E. Ungnade and L. W. Kissinger, *Tetrahedron* 19, Suppl. 1, 143 (1963).<sup>84</sup> P. Walstra, W. P. Trompen, and J. T. Hackmann, *Recl. Trav. Chim. Pays-Bas* 87, 452 (1968).<sup>85</sup> A. J. Boulton, P. Hadjimihalakis, A. R. Katritzky, and A. Majid Hamid, *J. Chem. Soc. C*, 1901 (1969).<sup>86</sup> A. R. Gagneux and R. Meier, *Helv. Chim. Acta* 53, 1883 (1970).



A variety of dialkyl, diaryl, and aromatic-fused furoxan spectra have been reported by Boyer *et al.*,<sup>74</sup> who sought to distinguish between "typical" furoxans ( $\lambda_{\max}$  255–285 nm) and " $\psi$ -*o*-dinitrosobenzenes" (as he designated the benzofuroxans) (350–410 nm). In view of the more extended conjugation in the chromophore of the benzofuroxans, the observed difference is not unexpected. The spectra of some other benzofuroxans<sup>37</sup> and diaroylfuroxans<sup>87</sup> are available.

Most of the above references simply provide data on absorption maxima. The spectra are depicted in detail for simple furoxans,<sup>83</sup> benzofuroxan<sup>88,89</sup> and its methoxy<sup>88</sup> and nitro<sup>89</sup> derivatives, and nitrobenzodifuroxan and benzotrifuroxan.<sup>89</sup> Meisenheimer complex formation in nitrobenzofuroxans is accompanied by ultraviolet spectral changes, whereby the kinetics and equilibria of the reactions can be measured. This work is mentioned in Section VIII.

### C. NUCLEAR MAGNETIC RESONANCE SPECTRA

The previous review<sup>6</sup> in this series summarized the early work on benzofuroxans using proton resonance techniques. Dynamic resonance effects (DNMR)—signal-broadening and coalescence phenomena at medium and fast exchange rates—are characteristic of furoxans fused to aromatic rings. More recent studies have included line-shape analyses using density-matrix methods for benzofuroxan<sup>90</sup> and its 5-fluoro<sup>91</sup> and other 5-halo derivatives.<sup>38</sup> These measurements allow the calculation of exchange rates over a range of temperatures, and thus provide the thermodynamic activation parameters for the reaction. Other systems with further heterocyclic ring fusion (**10**, **11**) have been investigated by line-shape analysis methods.<sup>72</sup> More qualitative results, on coalescence temperatures and/or equilibrium

<sup>87</sup> D. A. Shirley, B. H. Gross, and M. J. Danzig, *J. Org. Chem.* **23**, 1024 (1958).

<sup>88</sup> A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.* **10**, 7 (1969).

<sup>89</sup> A. S. Bailey and J. R. Case, *Tetrahedron* **3**, 113 (1958).

<sup>90</sup> K.-I. Dahlqvist and S. Forsen, *J. Magn. Reson.* **2**, 61 (1970). (In Table I of this paper the chemical shift of H-4 in  $\text{CD}_2\text{Cl}_2$  should be 7.63 p.p.m.)

<sup>91</sup> S. Uematsu and Y. Akahori, *Chem. Pharm. Bull.* **25**, 3261 (1977).

constants, are available for a wide range of substituted benzofuroxans and other furoxans fused to heterocyclic rings. The results of these studies are discussed in Section V.B.

In the unfused series, and in furoxans fused to nonaromatic rings, proton resonance has proved invaluable for structure identification. Englert<sup>92</sup> and Mallory and Cammarata<sup>31</sup> suggested that, of the two signals shown by dimethylfuroxan, the upfield resonance should be ascribed to the 3-methyl and the downfield to the 4-methyl group. The chemical shift separation is approximately 0.22 ppm, and the low-field signal is close to that of dimethylfuran. The structures of many isomeric pairs of methyl-substituted furoxans have been assigned on this basis,<sup>79,85,93-96</sup> the correctness of which has been confirmed by X-ray crystallography of one or both of the isomers in several instances (viz., the *p*-bromophenyl,<sup>41,42,85</sup> carbamoyl,<sup>43,79</sup> *N,N*-dimethylcarbamoyl,<sup>44,45,79</sup> carbazoyl,<sup>46,79</sup> phenylsulfonyl,<sup>49,79</sup> and nitro<sup>51,79</sup> derivatives, and the cyclic ketone<sup>760,80</sup>). The bridgehead protons of some more rigidly fused furoxans (e.g., **12**, **13**) show a much smaller chemical shift difference (0.04 ppm),<sup>97</sup> which seems therefore to be susceptible to conformational effects.



(10) X = S

(11) X = NMe



(12)



(13a)



(13b)

In benzofuroxan the chemical shift difference between the 4- and 7-protons is approximately 0.25 ppm, with that adjacent to the *N*-oxide group appearing at higher field. The 5- and 6-protons show a smaller shift (0.16 ppm) in the same direction—that at the position in conjugation with the *N*-oxide group is at higher field.<sup>90,98,99</sup> Similar shift differences are found in many

<sup>92</sup> G. Englert, *Z. Anal. Chem.* **181**, 447 (1961).

<sup>93</sup> A. Gasco, V. Mortarini, G. Ruà, G. M. Nano, and E. Menziani, *J. Heterocycl. Chem.* **9**, 577 (1972).

<sup>94</sup> A. Gasco, V. Mortarini, G. Ruà, and E. Menziani, *J. Heterocycl. Chem.* **9**, 837 (1972).

<sup>95</sup> A. Gasco, V. Mortarini, G. Ruà, and A. Serafino, *J. Heterocycl. Chem.* **10**, 587 (1973).

<sup>96</sup> A. Gasco, V. Mortarini, and E. Reynaud, *Farmaco, Ed. Sci.* **28**, 624 (1973).

<sup>97</sup> J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton, and R. C. Brown, *J. C. S. Perkin I*, 1587 (1972). (On p. 1590 the numbering of the positions 4 and 7 in the text is inconsistent with that in the structure, and should be reversed.)

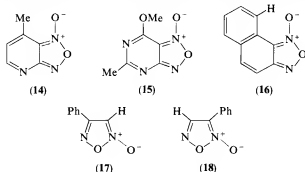
<sup>98</sup> R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.*, 197 (1963).

<sup>99</sup> F. B. Mallory, S. L. Manatt, and C. S. Wood, *J. Am. Chem. Soc.* **77**, 5433 (1965).



fused<sup>72,100-102</sup> and substituted<sup>38,39,91,92,103,104</sup> benzofuroxans (although occasionally exceptions are found<sup>105</sup>), and in heteroaromatic-ring-fused furoxans.<sup>102,104</sup>

The *N*-oxide group exerts a shielding influence also on more distant protons, but the effect is attenuated. Thus, the methyl groups adjacent to the furoxan rings in structures **12**, **13b**, and **14** appear upfield of the corresponding groups in the isomeric oxides, by 0.10,<sup>97</sup> 0.03,<sup>97</sup> and 0.02 ppm,<sup>104</sup> respectively, and the methoxy protons in **15** are 0.055 ppm upfield of the signal in the 3-oxide.<sup>106</sup> In **16**, however, the 9-H is approximately 0.5 ppm downfield of that in the 3-oxide,<sup>100</sup> and other cases of deshielding in 4-substituted benzofuroxans are known.<sup>105</sup> Examples of protons directly attached to the furoxan ring are few (see Section VI); in the two monophenyl isomers, the 3-H in **17** absorbs at  $\delta$  7.26 ppm, the 4-H in **18** at 8.55 (in CDCl<sub>3</sub>).<sup>107,108</sup>



The ortho proton-proton coupling constants in benzofuroxan show the expected alternation in magnitude, following the bond orders between the carbon atoms.<sup>90,98,99</sup> Substituent effects on coupling constants have been correlated in a series of benzo-fused heterocycles, including benzofuroxan.<sup>109</sup> The proton resonance spectrum of benzofuroxan in a nematic solvent has been published (somewhat obscurely).<sup>110</sup>

<sup>100</sup> M. Altaf-ur-Rahman, A. J. Boulton, D. P. Clifford, and G. J. T. Tiddy, *J. Chem. Soc., B*, 1516 (1968).

<sup>101</sup> A. J. Boulton, A. C. G. Gray, and A. R. Katritzky, *J. Chem. Soc.*, 5958 (1965).

<sup>102</sup> A. J. Boulton and D. Middleton, *J. Org. Chem.* **39**, 2956 (1974).

<sup>103</sup> A. J. Boulton, A. R. Katritzky, M. J. Sewell, and B. Wallis, *J. Chem. Soc., B*, 914 (1967).

<sup>104</sup> A. J. Boulton, P. J. Halls, and A. R. Katritzky, *J. Chem. Soc., B*, 636 (1970).

<sup>105</sup> A. J. Boulton, K. W. Thoe, S. N. Balasubrahmanyam, I. M. Mallick, and A. S. Radhakrishna, *J. Org. Chem.* **45**, 1653 (1980).

<sup>106</sup> R. Nutiu and A. J. Boulton, *J. C. S. Perkin I*, 1327 (1976).

<sup>107</sup> A. Gasco and B. Ferrarotti, unpublished results (1979).

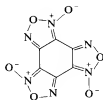
<sup>108</sup> J. V. Burakevich, A. M. Lore, and G. P. Volpp, *J. Org. Chem.* **36**, 5 (1971).

<sup>109</sup> A. R. Katritzky and Y. Takeuchi, *J. C. S. Perkin II*, 1682 (1972).

<sup>110</sup> P. Diehl and C. Khetrapal, *Proc. Colloq. AMPERE* **15**, 251 (1968) [*CA* **72**, 17085 (1970)].

Both  $^{17}\text{O}$  and  $^{15}\text{N}$  resonances reveal the presence of different types of oxygen<sup>111</sup> and nitrogen,<sup>112</sup> respectively, in dimethylfuroxan and in benzofuroxan, with DNMR effects at higher temperatures for the latter compound. The  $^{15}\text{N}$  resonances appear at +7.0 and +19.0 ppm from  $\text{HNO}_3$  (dimethylfuroxan) and at -1.7 and +11.8 ppm (benzofuroxan, at -26°). The high-field signal of dimethylfuroxan shifts to higher field in acidic solvents, while the lower field signal remains constant. Since similar shifts are found for the  $^{15}\text{N}$  signals of dimethylfurazan and benzofurazan, it was suggested that the dicoordinate nitrogen gives the higher field signal.<sup>112</sup> However, the shifts of the furazans in acetone (-31.0, -42.5 ppm) are well downfield of both furoxan signals, and it seems that further work is needed to confirm (or otherwise) this conclusion. The  $^{14}\text{N}$  spectra have also been reported for the two furoxans above,<sup>113-115</sup> for diacetyl-, diethyl-, diaryl-, and dihalofuroxans,<sup>115</sup> and also for benzotrifuroxan.<sup>114,115</sup> In all cases only a single very broad signal was seen. This should not, however, be attributed to rapid exchange (cf. Ref. 114).

The carbon atoms of the furoxan ring show a remarkably large chemical shift difference in the  $^{13}\text{C}$  spectra: the  $\delta$  values are 156.1 and 113.8 ppm for dimethylfuroxan, and 152.2 and 113.7 ppm for benzofuroxan, with coalescence to a single signal at higher temperatures in the latter case. The low-field signals are close to those of the corresponding furazans (152.2 and 148.6 ppm, respectively), and on this ground were assigned to the carbons attached to the dicoordinate nitrogens.<sup>116</sup> The two separate signals in the  $^{13}\text{C}$  spectrum of benzotrifuroxan confirm its structure as **19**.<sup>117</sup>



(19)

<sup>111</sup> H. A. Christ, P. Diehl, H. R. Schneider, and H. Dahn, *Helv. Chim. Acta* **44**, 865 (1961); P. Diehl, H. A. Christ, and F. B. Mallory, *ibid.* **45**, 504 (1962).

<sup>112</sup> I. Yavari, R. E. Botto, and J. D. Roberts, *J. Org. Chem.* **43**, 2542 (1978).

<sup>113</sup> G. Englert, *Z. Elektrochem.* **65**, 854 (1961).

<sup>114</sup> J. Mason, W. van Bronswijk, and J. G. Vinter, *J. C. S. Perkin II*, 469 (1977).

<sup>115</sup> M. Witanowski, L. Stefaniak, A. Grabowska, and G. A. Webb, *Spectrochim. Acta* **34A**, 877 (1978).

<sup>116</sup> F. A. L. Anet and I. Yavari, *Org. Magn. Reson.* **8**, 158 (1976).

<sup>117</sup> L. Stefaniak, M. Witanowski, and G. A. Webb, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **26**, 281 (1978) [*CA* **89**, 128704 (1978)].

## D. MASS SPECTRA

Apart from routine analytical use, and occasional publications dealing with individual compounds, the mass spectra of furoxans have not received much attention. Ungnade and Loughran<sup>118</sup> investigated some half-dozen simple furoxans, two somewhat contradictory reports on the spectrum of benzofuroxan have appeared,<sup>119,120</sup> and other brief accounts, covering a limited range of structural types, have been published.<sup>85,97,121</sup> Unlike most aromatic N-oxides, the  $(M - 16)^+$  ion is frequently weak, and only rarely is oxygen loss a major fragmentation route. Characteristically, ions occur at  $(M - NO)^+$ ,  $(M - N_2O_2)^+$ , and at 30 ( $NO^+$ ) amu which are rationalized by assuming prior ring opening to the dinitroso compound (cf. Section V,B) followed by cleavage of one or both of the N—C bonds. This would render mass spectrometry useless for the identification of isomers when the position of the exocyclic oxygen is in question. Parent ions ( $M^+$ ) are usually prominent unless the substituents are prone to fragmentation; in some cases  $(M + 1)^+$  ions, arising from hydrogen transfer reactions, are of comparable intensity.<sup>97</sup> The ion  $(M - NO_2)^+$  may be prominent in the benzofuroxan spectrum.<sup>119</sup> The spectrum of benzotrifuroxan (**19**) has been analyzed in some detail and compared with that of the trifurazan.<sup>121</sup>

## E. OTHER PHYSICAL PROPERTIES

Tables of melting points and/or boiling points of furoxans<sup>3</sup> and their fused derivatives<sup>3,6</sup> have been published. Among other thermochemical measurements, the heats of combustion have been the most widely investigated. Early work of Milone<sup>122</sup> compared heats of combustion for aryl methyl furoxan and "peroxide" isomers (now known to be 4-aryl-3-methyl and 3-aryl-4-methyl furoxans, respectively<sup>85</sup>). The latter were found to be considerably the more exothermic, by  $\sim 33 \text{ kJ mol}^{-1}$ , which is at variance with the finely balanced equilibria between the isomers (Section V,B) (although these were measured in solution, and heats of solution have not been compared). More recently, the heats of combustion of dimethylfuroxan,<sup>123</sup> benzo-

<sup>118</sup> H. E. Ungnade and E. D. Loughran, *J. Heterocycl. Chem.* **1**, 61 (1964).

<sup>119</sup> N. Bild and M. Hesse, *Helv. Chim. Acta* **50**, 1885 (1967).

<sup>120</sup> R. A. Abramovitch, E. P. Kyba, and E. F. V. Scriven, *J. Org. Chem.* **36**, 3796 (1971).

<sup>121</sup> A. S. Bailey, C. J. W. Gutch, J. M. Peach, and W. A. Waters, *J. Chem. Soc., B*, 681 (1969).

<sup>122</sup> M. Milone, *Gazz. Chim. Ital.* **61**, 153 (1931).

<sup>123</sup> Yu. N. Matyushin, V. I. Pepekin, S. P. Golova, T. I. Godovikova, and L. I. Khmel'nitskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 181 (1971) [*CA* **75**, 26138 (1971)].

furoxan,<sup>124</sup> and bis(hydroxymethyl)furoxan dinitrate (**1**;  $R^1 = R^2 = \text{CH}_2\text{ONO}_2$ )<sup>125</sup> have been compared with those of the corresponding furazans, to give fairly consistent values ( $247 \pm 4 \text{ kJ mol}^{-1}$ ) for the energy of the  $\text{N}^+ - \text{O}^-$  bond. Heats of combustion and enthalpies of formation have also been determined for a number of dialkyl-,<sup>126</sup> methylnitro-,<sup>127</sup> and dicyano-<sup>128</sup> furoxans, and of benzotrifuroxan.<sup>129</sup> The trifuroxan (**19**), which is classed as an experimental explosive, has been studied with respect to its detonation kinetics,<sup>129,130</sup> thermal release,<sup>131</sup> and rate of thermal decomposition.<sup>132</sup> Differential thermogravimetric analysis has been applied to the potassium "salt" (which is also explosive; see Section VIII) of 4,6-dinitro-benzofuroxan,<sup>133</sup> and detonation<sup>134</sup> and voltage breakdown studies on the "dielectric strength" of the same compound<sup>135</sup> have been made. The thermal decomposition kinetics of an amino-nitro-furoxan have been measured,<sup>136</sup> and also the detonation properties of 3-methyl-4-nitrofuroxan.<sup>127</sup>

The X-ray photoelectron spectrum of benzotrifuroxan shows the two different types of carbon, nitrogen, and oxygen atoms that are present.<sup>137</sup>

Electrochemical reduction (see also Section V,D,5) of furoxans produces radical-anions derived from the reduction products (e.g., the benzofurazan radical-anion, from benzofuroxan), as shown by the electron spin resonance (ESR) spectra.<sup>138</sup> Benzotrifuroxan (**19**) gives a radical-anion showing a

<sup>124</sup> V. I. Pepekin, Yu. N. Matyushin, A. G. Feshchenko, S. P. Smirnov, and A. Ya. Apin, *Dokl. Akad. Nauk SSSR* **202**, 91 (1972) [*CA* **76**, 90904 (1972)].

<sup>125</sup> V. I. Pepekin, Yu. N. Matyushin, A. D. Nikolaeva, A. P. Kirsanov, L. V. Platonova, and Yu. A. Lebedev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1870 (1975) [*CA* **84**, 4243 (1976)].

<sup>126</sup> Yu. N. Matyushin, V. I. Pepekin, A. D. Nikolaeva, N. M. Lyapin, L. V. Nikolaeva, A. V. Artyushin, and A. Ya. Apin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 842 (1973) [*CA* **79**, 42422 (1973)].

<sup>127</sup> A. D. Nikolaeva, Yu. N. Matyushin, V. I. Pepekin, V. S. Smelov, V. V. Bulidorov, T. I. Bulidorova, and A. Ya. Apin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 965 (1972) [*CA* **77**, 75165 (1972)].

<sup>128</sup> E. C. Lupton and G. Hess, *J. Chem. Eng. Data* **20**, 135 (1975) [*CA* **83**, 16659 (1975)].

<sup>129</sup> P. E. Rouse, *J. Chem. Eng. Data* **21**, 16 (1976) [*CA* **84**, 92352 (1976)].

<sup>130</sup> R. N. Rogers, *Thermochim. Acta* **11**, 131 (1975) [*CA* **82**, 142281 (1975)].

<sup>131</sup> D. L. Ornellas, *Combust. Flame* **23**, 37 (1974) [*CA* **81**, 172463 (1974)].

<sup>132</sup> P. B. Bailey, *Combust. Flame* **23**, 329 (1974) [*CA* **82**, 142280 (1975)].

<sup>133</sup> R. L. Graybush, F. G. May, and A. C. Forsyth, *Thermochim. Acta* **2**, 153 (1971) [*CA* **74**, 143965 (1971)]; *Natl. Bur. Stand. (U.S.), Spec. Publ.* **338**, 151 (1973) [*CA* **79**, 80981 (1973)].

<sup>134</sup> H. Rathsburg and H. Stadler, *Explosivstoffe* **6**, 67 (1958) [*CA* **53**, 718 (1959)].

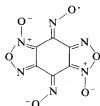
<sup>135</sup> L. Avrami and H. J. Jackson, *U.S. N. T. I. S., AD Rep.* **AD-747364** (1972) [*CA* **78**, 113516 (1973)].

<sup>136</sup> V. V. Zverev, I. Sh. Saifullin, and G. P. Sharmin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 313 (1978) [*CA* **88**, 169377 (1978)].

<sup>137</sup> J. Bus, *Recl. Trav. Chim. Pays-Bas* **91**, 552 (1972).

<sup>138</sup> S. P. Solodovnikov and Z. V. Todres, *Khim. Geterotsikl. Soedin.*, 811 (1967) [*CA* **68**, 114511 (1968)].

five-line spectrum ( $a_N$  4.53 G, in DMF) to which the structure **20** was assigned.<sup>121</sup>



(20)



(21)

The dipole moments of a number of alkyl- and aryl-substituted furoxans have been recorded.<sup>139</sup> The values fall in the range 4.6–5.5 D, for the isomers formerly assigned furoxan and “peroxide” structures alike. Auwers studied their optical properties,<sup>140</sup> and other early publications detail some cryoscopic<sup>141</sup> and crystallographic<sup>142</sup> measurements on furoxans and benzofuroxans.

4,6-Dinitrobenzofuroxan, nitrobenzodifuroxan (**21**), and benzotrifuroxan form complexes with a wide variety of compounds.<sup>89,143–147</sup> In nonaqueous solutions benzotrifuroxan can be titrated as an acid against tetrabutylammonium hydroxide; however, the nature of the interaction, which seems to involve between one and two hydroxide ions per molecule of trifuroxan, is not known.<sup>148</sup>

#### IV. Preparation of Furoxans

The previous reviews<sup>3–5</sup> covered the principal synthetic routes to furoxans and benzofuroxans before 1960, and, apart from occasional curiosities, none of the considerable number of preparations since that time breaks significantly new ground.

<sup>139</sup> E. Borello and G. Lanfranco, *Atti Accad. Sci. Torino, Cl. Sci. Fis., Mat. Nat.*, **93**, 466 (1958–1959); G. Tappi and V. di Vajo, *Gazz. Chim. Ital.*, **69**, 615 (1939).

<sup>140</sup> K. von Auwers, *Ber. Dtsch. Chem. Ges.*, **60**, 2122 (1927); **61**, 1041 (1928).

<sup>141</sup> G. Ponzio and M. Milone, *Gazz. Chim. Ital.*, **58**, 844 (1928); M. Milone, *ibid.*, **59**, 266 (1929); G. Tappi and A. Demorra, *ibid.*, **69**, 708 (1939).

<sup>142</sup> M. Milone, *Gazz. Chim. Ital.*, **60**, 632 (1930).

<sup>143</sup> A. S. Bailey, *J. Chem. Soc.*, 4710 (1960).

<sup>144</sup> B. Kamenar and C. K. Prout, *J. Chem. Soc.*, 4838 (1965).

<sup>145</sup> C. K. Prout and H. M. Powell, *J. Chem. Soc.*, 4882 (1965).

<sup>146</sup> H. A. O. Hill, A. J. Macfarlane, B. E. Mann, and R. J. P. Williams, *J. C. S. Chem. Commun.*, 123 (1968).

<sup>147</sup> W. Selig, *Lawrence Livermore Lab. [Rep.] UCID-17450* (1977) [*CA* **88**, 74344 (1978)].

<sup>148</sup> W. Selig, *Fresenius' Z. Anal. Chem.*, **289**, 44 (1978).

## A. DIMERIZATION OF NITRILE OXIDES

1. *From Isolated Nitrile Oxides*

The dimerization of aromatic and aliphatic nitrile oxides to furoxans is a general route to symmetrically disubstituted derivatives ( $\mathbf{1}$ ;  $\mathbf{R}^1 = \mathbf{R}^2$ ) of this heterocycle. For unsymmetrical substitution a mixed reaction can be performed,<sup>57</sup> but there is little to recommend this, from a preparative point of view. The reaction was first described by Werner,<sup>149</sup> although nitrile oxides were unrecognized intermediates in a number of preparations prior to that time, back to the earliest of Kekulé.<sup>1</sup> The dimerization occurs on heating the nitrile oxide, or simply allowing it to stand, in a neutral medium, and it usually proceeds so readily that isolation and conservation of the oxide are generally difficult. It is a reversible reaction (see Section V.A), and it proceeds in competition with the rearrangement of the oxide to the isocyanate. The influence of the nature of the substituent and the conditions required for the dimerization on the rate of the reaction have been qualitatively discussed by Grundmann and Grünanger.<sup>150</sup> The question of steric hindrance to dimerization has received some attention. Generally, the dimerization of nitrile oxides heavily substituted near the functional group is slower than that of simpler types,<sup>151-155</sup> but even mesitonitrile oxide<sup>152</sup> and adamantane-1-carbonitrile oxide<sup>155</sup> form the expected furoxans under appropriate conditions, and there is no evidence that steric effects influence the course of the reaction. Second-order kinetics are followed, and solvent and substituent effects on the rate have been studied.<sup>151,154</sup> The substituent effects follow a Hammett relationship ( $\rho = +0.87$ ). Solvent dependence is low, and the entropy of activation is negative (approximately  $-80 \text{ J K}^{-1} \text{ mol}^{-1}$ ).<sup>154</sup> Base catalysis has been reported.<sup>156</sup>

The dimerization mechanism has been the subject of some discussion. The above data are in the main consistent with a one-step concerted cycloaddition process.<sup>154</sup> However, the mode of dimerization is contrary to that which would be expected on the basis of the principle of maximum gain in  $\sigma$ -bond energy, and an alternative two- (or three-) step mechanism has been

<sup>149</sup> A. Werner and H. Buss, *Ber. Dtsch. Chem. Ges.*, **27**, 2193 (1894).

<sup>150</sup> C. Grundmann and P. Grünanger, "The Nitrile Oxides," p. 62. Springer-Verlag, Berlin and New York, 1971.

<sup>151</sup> A. Dondoni, A. Mangini, and S. Ghersetti, *Tetrahedron Lett.*, 4789 (1966).

<sup>152</sup> C. Grundmann, H. D. Frommelt, K. Flory, and S. K. Datta, *J. Org. Chem.*, **33**, 1464 (1968).

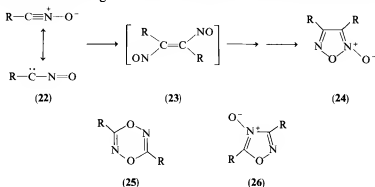
<sup>153</sup> B. J. Wakefield and D. J. Wright, *J. Chem. Soc. C*, 1165 (1970).

<sup>154</sup> G. Barbaro, A. Battaglia, and A. Dondoni, *J. Chem. Soc. B*, 588 (1970).

<sup>155</sup> A. Dondoni, G. Barbaro, A. Battaglia, and P. Giorgianni, *J. Org. Chem.*, **37**, 3196 (1972).

<sup>156</sup> H. Wieland, *Ber. Dtsch. Chem. Ges.*, **40**, 1667 (1907).

suggested,<sup>152,157</sup> in which the initial, product-determining, stage is the formation of the C—C bond, with the nitrile oxide being formally regarded as a nitrosocarbene (**22**). The dinitrosoolefin (**23**), possibly initially in the trans configuration, as shown, may isomerize and cyclize to form the furoxan (**24**). Analogy for the “nitrosocarbene” mode of addition of nitrile oxides is known.<sup>158</sup> A theoretical treatment of the reaction by the frontier molecular orbital approach,<sup>159</sup> and by the two-step radical cycloaddition theory,<sup>160</sup> would throw further light on whether consideration of **22** and **23** is necessary.



Other modes of dimerization of nitrile oxides have been observed. With Lewis acid catalysis 1,4,2,5-dioxadiazines (**25**) can be produced,<sup>161</sup> and 1,2,4-oxadiazole-4-oxides (**26**) may arise in the presence of a high alkali concentration.<sup>85</sup> Fulminic acid (HCNO) forms a variety of oligomers, but no furoxan (**24**; R = H) is isolated,<sup>5</sup> and phenylglyoxylonitrile oxide (PhCO·CNO) forms a second product, reportedly a tetramer (see Section IV.A.2). But these are exceptional cases; usually it is only dimerization to the furoxan that is observed.

Further examples of the dimerization of isolated nitrile oxides have been reported.<sup>162-168</sup>

<sup>157</sup> R. Huisgen, *Angew. Chem.* **75**, 742 (1963).

<sup>158</sup> G. Lo Vecchio, G. Grassi, F. Risitano, and F. Foti, *Tetrahedron Lett.*, 3777 (1973).

<sup>159</sup> G. Klopman, ed., "Chemical Reactivity and Reaction Paths." Wiley, New York, 1974.

<sup>160</sup> R. A. Firestone, *Tetrahedron* **33**, 3009 (1977).

<sup>161</sup> S. Morrocchi, A. Ricca, A. Selva, and A. Zanarotti, *Gazz. Chim. Ital.* **99**, 165 (1969).

<sup>162</sup> F. Eloy, *Bull. Soc. Chim. Belg.* **73**, 639 (1964).

<sup>163</sup> G. Zinner and H. Günther, *Angew. Chem., Int. Ed. Engl.* **3**, 383 (1964).

<sup>164</sup> C. Grundmann, V. Mini, J. M. Dean, and H. D. Frommelt, *Justus Liebigs Ann. Chem.* **687**, 191 (1965).

<sup>165</sup> Y. Imai, M. Akiyama, K. Uno, and Y. Iwakura, *Makromol. Chem.* **95**, 275 (1966).

<sup>166</sup> Y. Iwakura and M. Akiyama, Japanese Patent 68/06,068 [*CA* **69**, 19815 (1968)].

<sup>167</sup> Y. Iwakura, K. Uno, S. Shiraishi, and T. Hongu, *Bull. Chem. Soc. Jpn.* **41**, 2954 (1968).

<sup>168</sup> M. Majewski, B. Serafin, and T. Oklesinska, *Rocz. Chem.* **51**, 975 (1977).

## 2. From Nitrolic Acids and Their Precursors

Aryl, alkyl, and acyl nitrolic acids (**27**) can form furoxans by loss of nitrous acid, either spontaneously,<sup>169,170</sup> on heating,<sup>171-173</sup> or by the action of sodium bicarbonate.<sup>174</sup> In addition, they are probably intermediates in a wide variety of other preparations involving nitric or nitrous acid, or oxides of nitrogen, and nitro compounds or their precursors.

The following transformations probably proceed via nitrolic acid intermediates: ethyl bromoacetate and benzyl bromide into diethoxycarbonylfuroxan and diphenylfuroxan, respectively, by sodium nitrite in dimethylformamide<sup>175</sup>; 3-methyl-1,4-benzoxazin-2-one (**28**) into bis(1,4-benzoxazin-2-on-3-yl)furoxan with nitric acid and sodium nitrite<sup>176</sup>; and the reaction of methyl ketones with nitric acid, promoted by sodium nitrite, to form diacylfuroxans.<sup>27,177</sup> This last reaction has been known for nearly a century and has been studied extensively in recent years.<sup>87,178-188</sup> A by-product of the reaction of acetophenone,<sup>27</sup> sometimes known as "Holleman's peroxide," has been assigned dimeric [**2** ( $R^1 = R^2 = \text{PhCO}$ )<sup>27,28</sup> or **26** ( $R = \text{PhCO}$ )<sup>189</sup>] or tetrameric (**29**)<sup>29</sup> structures. Of these, the tetramer is the most likely, the infrared evidence being particularly persuasive, but final proof still has to be obtained. The formation of some analogs of **29** has been reported,<sup>188</sup> but it was not specified which ones, and no other details were given. (See also Appendix, Section X.)

<sup>169</sup> H. Wieland, *Ber. Dtsch. Chem. Ges.* **42**, 803 (1909).

<sup>170</sup> G. Ruggeri, *Gazz. Chim. Ital.* **55**, 72 (1925).

<sup>171</sup> M. Z. Jovitchitch, *Ber. Dtsch. Chem. Ges.* **35**, 151 (1902).

<sup>172</sup> R. Behrend and H. Tryller, *Justus Liebigs Ann. Chem.* **283**, 209 (1894).

<sup>173</sup> L. I. Peterson, *Tetrahedron Lett.*, 1727 (1966).

<sup>174</sup> R. Behrend and J. Schmitz, *Justus Liebigs Ann. Chem.* **277**, 310 (1893).

<sup>175</sup> N. Kornblum and W. Weaver, *J. Am. Chem. Soc.* **80**, 4333 (1958).

<sup>176</sup> E. Biekert and H. Kössel, *Justus Liebigs Ann. Chem.* **662**, 93 (1963).

<sup>177</sup> G. Ponzio, *Gazz. Chim. Ital.* **56**, 490 (1926).

<sup>178</sup> H. R. Snyder and N. E. Boyer, *J. Am. Chem. Soc.* **77**, 4233 (1955), and references therein.

<sup>179</sup> M. S. Chang and A. J. Matuszko, *J. Org. Chem.* **26**, 5239 (1961).

<sup>180</sup> C. A. Howe and A. Howe, *J. Chem. Soc.*, 6064 (1963).

<sup>181</sup> M. S. Chang, *J. Org. Chem.* **28**, 3542 (1963).

<sup>182</sup> C. R. Meloy and D. A. Shirley, *J. Org. Chem.* **32**, 1255 (1967).

<sup>183</sup> M. S. Chang and J. U. Lowe, *J. Org. Chem.* **33**, 866 (1968).

<sup>184</sup> T. Nakagome and R. N. Castle, *J. Heterocycl. Chem.* **5**, 379 (1968).

<sup>185</sup> Y. Matsuki and Y. Adachi, *Nippon Kagaku Zasshi* **89**, 192 (1968) [*CA* **69**, 67165 (1968)].

<sup>186</sup> G. C. Brophy, S. Sternhell, N. M. D. Brown, I. Brown, K. J. Armstrong, and M. Martin-Smith, *J. Chem. Soc. C*, 933 (1970).

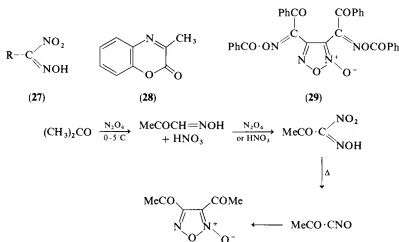
<sup>187</sup> R. Royer, P. Demerseman, and S. Risse, *Bull. Soc. Chim. Fr.*, 1691 (1974).

<sup>188</sup> H. Tondys and J. Lange, *Acta Pol. Pharm.* **34**, 569 (1977).

<sup>189</sup> R. Scarpati and M. Rippa, *Gazz. Chim. Ital.* **88**, 804 (1958).



Dinitrogen tetroxide can be used to convert both aliphatic and aromatic methyl ketones into diacylfuroxans. For acetone the route of Scheme 1 was proposed; the nitrolic acid was identified by its infrared spectrum, and the nitrile oxide was trapped as its 1,3-dipolar cycloadduct with dimethyl acetylenedicarboxylate.<sup>173</sup>



SCHEME 1

Aldoximes and nitrogen oxides form furoxans in variable yields<sup>4</sup>; dinitrogen tetroxide is the most convenient reagent.<sup>190-194</sup> The nitrolic acids (27; R = alkyl) can be isolated when aliphatic aldoximes are used<sup>192</sup>; otherwise the furoxans are formed directly. With polyfluorinated aldoximes fuming nitric acid is effective.<sup>195</sup>

Further oxidation ( $\text{N}_2\text{O}_4$ ) of the dehydro dimers  $[(\text{ArCH}:\text{NO})_2]$  of aromatic aldoximes produces furoxans.<sup>196</sup> Here the nitrolic acids may not be intermediates, as there are alternative routes to the nitrile oxides.<sup>197</sup> Some authors have assumed that the formation of furoxans in this reaction

<sup>190</sup> R. Scholl, *Ber. Dtsch. Chem. Ges.* **23**, 3490 (1890).

<sup>191</sup> G. Ponzio, *Gazz. Chim. Ital.* **36**, 287, 588 (1906).

<sup>192</sup> S. S. Novikov, L. I. Khmel'nitskii, and O. V. Lebedeva, *Zh. Obshch. Khim.* **28**, 2296 (1958) [*CA* **53**, 3111 (1959)].

<sup>193</sup> J. H. Boyer and H. Alul, *J. Am. Chem. Soc.* **81**, 4237 (1959).

<sup>194</sup> H. G. Adolph, *J. Org. Chem.* **40**, 2626 (1975).

<sup>195</sup> R. M. Scribner, *J. Org. Chem.* **29**, 279 (1964).

<sup>196</sup> H. Kropf and R. Lambeck, *Justus Liebigs Ann. Chem.* **700**, 18 (1966).

<sup>197</sup> C. Grundmann and G. F. Kite, *Synthesis*, 156 (1973).

has a bearing on the problem of the structure of the dimers, which has been a much-debated question,<sup>196-201</sup> but this seems unsound.

Other furoxan preparations, probably via nitrolic acids, include those of diphenylfuroxan from phenylglyoxylic acid oxime ( $N_2O_4$ ),<sup>202</sup> di(4-pyrimidyl)furoxan from 4-methylpyrimidine ( $HNO_3$ ),<sup>203</sup> bis(arylamino-carbonyl)furoxans from  $\alpha$ -oximinoacetoacetanilides ( $HNO_3/NaNO_2$ ),<sup>78</sup> and dialkoxycarbonylfuroxans from dialkyl acetone-1,3-dicarboxylates ( $HNO_3/N_2O_3$ ).<sup>204</sup> A diindoxazenylfuroxan can be isolated from the reaction of indoxazene-3-acetic acid with nitric acid.<sup>205</sup> It is possible that some of the reactions noted in the next section, which are considered as nitromethyl dehydrations, proceed at least in part by nitrous acid catalysis with nitrolic acids as intermediates.

### 3. From Nitroalkanes

Primary nitro compounds ( $RCH_2NO_2$ ) produce nitrile oxides on dehydration, and in the absence of a dipolarophile these usually dimerize to furoxans. As dehydrating agents, phenyl isocyanate<sup>206,207</sup> or acetic anhydride<sup>208</sup> in the presence of catalytic triethylamine, diketene,<sup>209</sup> and sulfuric acid<sup>210</sup> have been used. Milder reagents can be employed when the  $\alpha$ -methylene group is additionally activated: diethoxycarbonylfuroxan is formed from ethyl nitroacetate with boron trifluoride etherate in acetic anhydride,<sup>211</sup> and bistrifluoromethylfuroxan from the corresponding nitroethane with trifluoroacetic anhydride and triethylamine.<sup>212</sup> Nitric acid in acetic acid converts aryl nitromethyl sulfones into bisarylsulfonylfuroxans.<sup>213</sup>

<sup>198</sup> L. I. Smith, *Chem. Rev.* **23**, 239 (1938).

<sup>199</sup> L. Horner, L. Hockenberger, and W. Kirmse, *Chem. Ber.* **94**, 290 (1961).

<sup>200</sup> G. Just and K. Dahl, *Tetrahedron* **24**, 5251 (1968).

<sup>201</sup> B. Unterhalt and U. Pindur, *Chimia* **27**, 210 (1973); U. Pindur and B. Unterhalt, *Arch. Pharm. (Weinheim, Ger.)* **312**, 282 (1979).

<sup>202</sup> G. Ponzio, *Gazz. Chim. Ital.* **39**, 324 (1909).

<sup>203</sup> S. Gabriel and J. Colman, *Ber. Dtsch. Chem. Ges.* **32**, 2921 (1899); **35**, 1569 (1902).

<sup>204</sup> B. Unterhalt and U. Pindur, *Arch. Pharm. (Weinheim, Ger.)* **309**, 781 (1976).

<sup>205</sup> H. Uno and M. Kurokawa, *Chem. Pharm. Bull.* **26**, 3498 (1978).

<sup>206</sup> T. Hoshino and M. Mukaikama, Japanese Patent 59/9855 [*CA* **54**, 7738 (1960)].

<sup>207</sup> M. Mukaikama and T. Hoshino, *J. Am. Chem. Soc.* **82**, 5339 (1960).

<sup>208</sup> A. Rahman, N. Razzaq, and A. Jabbar, *Pak. J. Sci. Res.* **30**, 91 (1978) [*CA* **90**, 203967 (1979)].

<sup>209</sup> S. Tsushima, T. Tsujikawa, and O. Aki, Japanese Patent 68/24,902 [*CA* **70**, 87344 (1969)].

<sup>210</sup> I. V. Vigalok, I. E. Moisek, and N. V. Svetlov, *Khim. Geterotsikl. Soedin.*, 175 (1969) [*CA* **71**, 3330 (1969)].

<sup>211</sup> K. Hirai, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull.* **20**, 97 (1972).

<sup>212</sup> A. M. Krzhizhevskii, N. S. Mirzubekeyants, Yu. A. Cheburkov, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2513 (1974) [*CA* **82**, 111513 (1975)].

<sup>213</sup> J. L. Kelley, E. W. McLean, and K. F. Williard, *J. Heterocycl. Chem.* **14**, 1415 (1977).

The acid-catalyzed formation of diacylfuroxans from long-chain  $\beta$ -ketonitroalkanes has been claimed.<sup>214</sup>

Nitro derivatives are probable intermediates in the following transformations: cyanoacetic acid into dicyanofuroxan ( $\text{HNO}_3/\text{H}_2\text{SO}_4/\text{F}_3\text{C}\cdot\text{CO}_2\text{H}$ )<sup>215</sup>; arenesulfonylacetic acids into bisarylsulfonylfuroxans ( $\text{HNO}_3/\text{AcOH}$ )<sup>216</sup>; sodium *p*-toluenesulfinate and chloropicrin into ditosylfuroxan<sup>216</sup>; benzylmercuric chloride into diphenylfuroxan ( $\text{HNO}_3$ )<sup>217</sup>; ethyl acetoacetate into diethoxycarbonylfuroxan ( $\text{AcONO}_2$ )<sup>218</sup>; methyl aroylacates into diaroylfuroxans ( $\text{HNO}_3/\text{CCl}_4$ )<sup>219</sup>; sydnonyl  $\beta$ -diketones into disydnonylfuroxans ( $\text{HNO}_3$  or  $\text{N}_2\text{O}_4$ )<sup>220</sup>; and dimethylacrylic esters into furoxandicarboxylic esters ( $\text{HNO}_3$ , or  $\text{HNO}_3/\text{H}_2\text{SO}_4$ ).<sup>221</sup> As mentioned above, simple dehydration of the aci form of the nitro compounds, with concomitant decarboxylation, deacylation, or reverse aldol reaction, accounts for the generation of the nitrile oxides; but in some cases  $\alpha$ -nitrosation of the nitro compound may provide an alternative pathway via the nitrolic acid.

#### 4. From Hydroxamic Acid Halides

Hydroxamic acid halides ( $\alpha$ -halooximes) are readily dehydrohalogenated by bases, generating the nitrile oxides. Sodium carbonate or alkali hydroxides,<sup>156,222-225</sup> amines,<sup>85,225-230</sup> and sodium acetate<sup>28</sup> are common

<sup>214</sup> R. G. Duranleau, J. M. Larkin, and S. R. Newman, U.S. Patent 4,089,867 (1978) [CA 89, 109515 (1978)].

<sup>215</sup> C. O. Parker, W. D. Emmons, H. A. Rolewicz, and K. S. McCallum, *Tetrahedron* 17, 79 (1962).

<sup>216</sup> W. V. Farrar, *J. Chem. Soc.*, 904 (1964).

<sup>217</sup> A. I. Titov and D. E. Rusanov, *Dokl. Akad. Nauk SSSR* 82, 65 (1952) [CA 47, 2688 (1953)].

<sup>218</sup> S. Sifniades, *J. Org. Chem.* 40, 3562 (1975); U.S. Patent 3,761,510 (1973) [CA 80, 14551 (1974)].

<sup>219</sup> Yu. S. Andreichikov, V. L. Gein, L. F. Gein, A. L. Fridman, and E. G. Yufareva, U.S.S.R. Patent 594,118 (1978) [CA 89, 43428 (1978)].

<sup>220</sup> A. L. Fridman, E. G. Yufareva, and N. A. Kolobov, *Khim. Geterotsikl. Soedin.*, 1692 (1977) [CA 88, 121061 (1978)].

<sup>221</sup> L. I. Bagal, A. A. Stotskii, and N. I. Novatskaya, *Zh. Org. Khim.* 3, 1201 (1967) [CA 67, 108160 (1967)].

<sup>222</sup> A. Werner, *Ber. Dtsch. Chem. Ges.* 27, 2846 (1894).

<sup>223</sup> C. D. Hurd, M. E. Nilson, and D. M. Wikholm, *J. Am. Chem. Soc.* 72, 4697 (1950).

<sup>224</sup> R. H. Wiley and B. J. Wakefield, *J. Org. Chem.* 25, 546 (1960).

<sup>225</sup> R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 2215 (1962).

<sup>226</sup> T. Mukaiyama, K. Saigo, and H. Takei, *Bull. Chem. Soc. Jpn.* 44, 190 (1971).

<sup>227</sup> A. Seher, *Chem. Ber.* 83, 400 (1950).

<sup>228</sup> J. M. J. Tronchet and Nghiep Le-Hong, *Carbohydr. Res.* 29, 311 (1973).

<sup>229</sup> J. M. J. Tronchet and F. Perret, *Carbohydr. Res.* 38, 169 (1974).

<sup>230</sup> I. N. Azerbaev, S. F. Khalilova, and I. P. Poplavskaya, *Zh. Org. Khim.* 11, 2302 (1975) [CA 84, 59324 (1976)].

reagents for this purpose, but silver<sup>149,231,232</sup> and mercury<sup>233</sup> salts have also been used. Silver nitrite converts the haloglyoximes **30** (R = Me, Ph) into substances formulated as the bicyclic peroxides **31**.<sup>234,235</sup> The same products arise by oxidation of the diacylfuroxan dioximes (**32**).<sup>236</sup> As was pointed out by Boyer,<sup>4</sup> even after adjustment of the six-membered ring to a furoxan moiety, these structures are clearly in need of revision.



(30)



(31)



(32)

### 5. From Diazo Compounds and Nitrosating Agents

Nitrosation of certain diazo compounds stabilized by substitution with electron-withdrawing groups is followed by loss of nitrogen, to give nitrile oxides, which dimerize to furoxans. Acyl<sup>188,220,237-241</sup> and perfluoroalkyl<sup>242</sup> diazomethanes with nitrogen oxides and  $\alpha$ -diazosulfones with dinitrogen trioxide<sup>239</sup> or nitrosyl chloride<sup>243</sup> react in this way. The presence of the electron-withdrawing group is necessary; simple diazoalkanes do not form furoxans.

### 6. From Fulminates and Halogens

The reaction of mercury fulminate (**33**; M = Hg/2) with a halogen gave the first furoxan (although misidentified) to be prepared,<sup>1</sup> and it was later

<sup>231</sup> A. Werner and W. Skiba, *Ber. Dtsch. Chem. Ges.* **32**, 1654 (1899).

<sup>232</sup> G. Ponzio and G. Charrier, *Gazz. Chim. Ital.* **37**, 65 (1907).

<sup>233</sup> I. De Paolini, *Gazz. Chim. Ital.* **60**, 700 (1930).

<sup>234</sup> G. Ponzio, *Gazz. Chim. Ital.* **62**, 424 (1932).

<sup>235</sup> G. Carbone, *Gazz. Chim. Ital.* **62**, 428 (1932).

<sup>236</sup> G. Ponzio and V. Bernardi, *Gazz. Chim. Ital.* **55**, 67 (1925).

<sup>237</sup> H. Wieland and C. Reisenegger, *Justus Liebigs Ann. Chem.* **401**, 244 (1913).

<sup>238</sup> A. R. Daniewski and T. Urbanski, *Rocz. Chem.* **42**, 289 (1968).

<sup>239</sup> J. F. J. Engbersen and J. B. F. N. Engberts, *Synth. Commun.* **1**, 121 (1971).

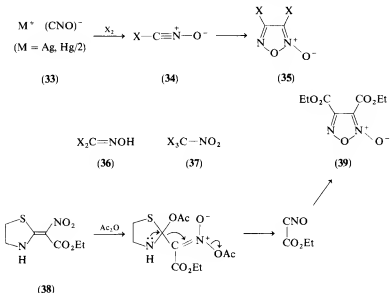
<sup>240</sup> A. L. Fridman and G. S. Ismagilova, U.S.S.R. Patent 350,795 (1972) [*CA* **78**, 16186 (1973)].

<sup>241</sup> H. Dahn, B. Favre, and J. P. Leresche, *Helv. Chim. Acta* **56**, 457 (1973).

<sup>242</sup> L. W. Kissinger, W. E. McQuiston, M. Schwartz, and L. Goodman, *Tetrahedron* **19**, Suppl. I, 131 (1963).

<sup>243</sup> J. C. Jagt, I. van Buuren, J. Strating, and A. M. van Leusen, *Synth. Commun.* **4**, 311 (1974).

extended to the silver and sodium salts.<sup>233,244-248</sup> Chlorine and bromine give mixtures of the furoxans (35) with the dihaloformaldoximes (36), and, particularly with excess of the halogen, chloro- or bromopicrin (37). Iodine and mercury fulminate,<sup>244,247,248</sup> or chlorine in ethyl chloride and silver fulminate,<sup>246</sup> give the dihalofuroxan as the main product. The haloformonitrile oxides (34) are probable intermediates. These can also be generated by dehydrohalogenation of the dihalo-oximes (36)<sup>233,249</sup> (which are accessible by other methods than through fulminates<sup>250</sup>).



## 7. From Miscellaneous Sources of Nitrile Oxides

Diphenylfuroxan is formed from the silver salt of phenylnitrosolic acid with iodine.<sup>251</sup> Nitrosation of dimethylphenacylsulfonium bromide ( $\text{HNO}_3/\text{NaNO}_2$ ) gives dibenzoylfuroxan.<sup>252</sup> With boron trifluoride etherate in

<sup>244</sup> E. Sell and R. Biedermann, *Ber. Dtsch. Chem. Ges.* **5**, 89 (1872).

<sup>245</sup> A. F. Holleman, *Ber. Dtsch. Chem. Ges.* **26**, 1403 (1893).

<sup>246</sup> H. Wieland, *Ber. Dtsch. Chem. Ges.* **42**, 4192 (1909).

<sup>247</sup> L. Birckenbach and K. Sennewald, *Justus Liebigs Ann. Chem.* **489**, 7 (1931).

<sup>248</sup> L. Birckenbach and K. Sennewald, *Ber. Dtsch. Chem. Ges.* **65**, 546 (1932).

<sup>249</sup> P. Bravo, G. Gaudiano, A. Quilico, and A. Ricca, *Gazz. Chim. Ital.* **91**, 47 (1961).

<sup>250</sup> E. Gryszkiewicz-Trochimowski, K. Dymowski, and E. Schmidt, *Bull. Soc. Chim. Fr.*, 597 (1948).

<sup>251</sup> H. Wieland and H. Bauer, *Ber. Dtsch. Chem. Ges.* **39**, 1480 (1906).

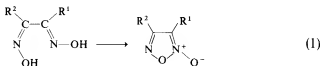
<sup>252</sup> Y. Otsuyi, Y. Tsujii, A. Yoshida, and E. Imoto, *Bull. Chem. Soc. Jpn.* **44**, 219 (1971).

acetic anhydride, 2-(carbethoxynitromethylene)thiazolidine (38) gives diethoxycarbonylfuroxan (39), possibly as shown.<sup>211</sup>

Irradiation of diphenylfuran in benzene, through Pyrex, with a high-pressure mercury lamp, affords benzonitrile (50%), 3,5-diphenyl-1,2,4-oxadiazole (10%), and diphenylfuroxan (14%).<sup>253</sup>

## B. DEHYDROGENATION OF DIOXIMES

Furoxans can be prepared by oxidation of  $\alpha$ -dioximes (Eq. 1). The method is suitable for both simple and aromatic-fused derivatives; the earliest fused compound in the series—naphtho[1,2-*c*]furoxan—was made in this way.<sup>15</sup> A wide variety of oxidizing agents have been used, including potassium ferricyanide,<sup>80,84,86</sup> halogens or alkali hypohalites,<sup>61,86,97,254–258</sup> nitric acid,<sup>83</sup> and nitrogen oxides<sup>83,108,126,259–261</sup>; the references cited are to more recent examples, the earlier literature being covered by Kaufman and Picard,<sup>3</sup> Boyer,<sup>4</sup> and Ponzio.<sup>26</sup> Other reagents which have been found effective are lead tetraacetate,<sup>196,262</sup> ceric ion,<sup>86</sup> phenyliodine(III)bistrifluoroacetate,<sup>263</sup> and *N*-oxides.<sup>264</sup> Electrochemical oxidation has also been used.<sup>265</sup> In addition to dioximes,  $\alpha$ -hydroxylaminooximes can be oxidized to furoxans (NaOBr).<sup>266</sup>



<sup>253</sup> T. Mukai, T. Oine, and A. Matsubara, *Bull. Chem. Soc. Jpn.* **42**, 581 (1969).

<sup>254</sup> G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* **13**, 1445 (1965).

<sup>255</sup> R. E. Havranek, G. B. Hoey, and D. H. Baeder, *J. Med. Chem.* **9**, 326 (1966).

<sup>256</sup> H. Reimann and H. Shneider, *Can. J. Chem.* **46**, 77 (1968).

<sup>257</sup> D. J. Chadwick, W. R. T. Cottrell, and G. D. Meakins, *J. C. S. Perkin I*, 655 (1972).

<sup>258</sup> H. Von Döbenek, E. Weil, E. Brunner, H. Deubel, and D. Wolkenstein, *Justus Liebig's Ann. Chem.*, 1424 (1978).

<sup>259</sup> M. Grifantini, F. Gualteri, S. Martelli, and M. L. Stein, *Ann. Chim. (Rome)* **58**, 200 (1968).

<sup>260</sup> G. Alimenti, M. Grifantini, F. Gualteri, and M. L. Stein, *Tetrahedron* **24**, 395 (1968).

<sup>261</sup> A. D. Nikolaeva and L. V. Kashevarova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **18**, 1550 (1975) [*CA* **84**, 59323 (1976)].

<sup>262</sup> Y. Yukawa and M. Sakai, *Nippon Kagaku Zasshi* **87**, 79 (1966) [*CA* **65**, 15366 (1966)].

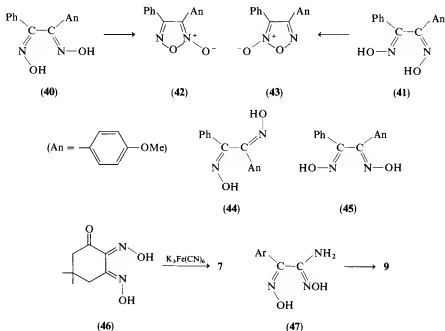
<sup>263</sup> S. Spyroudis and A. Varvoglis, *Synthesis*, 445 (1975).

<sup>264</sup> V. I. Vladykin, N. M. Konova, V. I. Markovskii, A. D. Nikolaeva, and S. I. Trakhtenberg, U.S.S.R. Patent 422,736 (1974) [*CA* **81**, 3946 (1974)].

<sup>265</sup> I. Tabakovic, M. Trkovnik, and D. Galijas, *J. Electroanal. Chem. Interfacial Electrochem.* **86**, 241 (1978) [*CA* **88**, 81015 (1978)].

<sup>266</sup> L. B. Volodarskii and L. A. Tikhonova, *Khim. Geterotsikl. Soedin.*, 748 (1975) [*CA* **83**, 164090 (1975)].

It would be surprising if a single mechanism were to encompass the wide variety of reagents that have been employed. The dinitrosoolefin has been suggested as an intermediate,<sup>267</sup> but this does not seem to be likely in all cases, in view of the fact that frequently the oxidation leads to a specific isomer, rather than a mixture of furoxans. The most careful investigation of this question was the earliest, of Meisenheimer *et al.*<sup>22</sup> They found that the two amphi forms [the  $\gamma$ -(40) and  $\delta$ -(41)] of *p*-methoxybenzil dioxime were specifically oxidized by ferricyanide to the furoxans 42 and 43, respectively, while the syn and anti isomers [the  $\alpha$ - (44) and  $\beta$ - (45) forms] gave mixtures of 42 and 43. Although, later, details of this work were criticized,<sup>26,268,269</sup> the overall conclusions stood. More recently, cases have been found of the highly stereospecific production of the less stable of a pair of furoxan isomers<sup>80,86</sup>; in both cases the dioxime configurations (46, 47) were deduced from the product structures, rather than proved independently.



Other oxime oxidations have been found to proceed stereospecifically,<sup>26,259,260</sup> while still others are nonstereospecific.<sup>83,108,259,260,270</sup>

<sup>267</sup> A. R. Katritzky and J. M. Lagowski, "The Chemistry of the Heterocyclic *N*-Oxides," p. 113. Academic Press, New York, 1971.

<sup>268</sup> G. Ponzio, *Ber. Dtsch. Chem. Ges.* **62**, 1750 (1929).

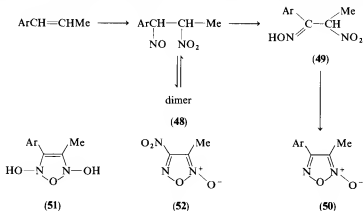
<sup>269</sup> C. R. Kinney, *J. Am. Chem. Soc.* **51**, 1592 (1929).

<sup>270</sup> J. V. Burakevich, A. M. Lore, and G. P. Volpp, *J. Org. Chem.* **36**, 1 (1971).

Anomalous behavior could be explained by assuming that the oxime configuration is altered under the reaction conditions, prior to cyclization, or that a different mechanism operates. Reports<sup>271,272</sup> that the several camphorquinone dioxime isomers all provide the same furoxan isomer are incorrect: the "camphorofuroxan" product has been shown to be an equimolar mixture of the two possible isomers (13).<sup>97</sup> It may be that the oxidation is stereospecific, but that isomer interconversion is unusually rapid in this case. The specificity may also depend on the reagent used. Dinitrogen tetroxide oxidizes three of the four possible phenylglyoxime isomers (the fourth is unknown) to 4-phenylfuroxan, but dilute nitric acid converts the  $\beta$ -isomer into the 3-phenyl compound (see Section VI). Many of the early results which were summarized by Ponzio<sup>26</sup> are of uncertain reliability.

### C. PREPARATIONS FROM OLEFINS AND NITROGEN OXIDES

This is another reaction in which the mechanism still has to be worked out. Early studies<sup>16,17,273-278</sup> of the action of nitrous acid on naturally occurring arylpropene derivatives (anethole, isosafrole, etc.) showed that a single isomer, the 3-methyl-4-arylfuroxan (**50**)<sup>85</sup> is formed, and that intermediate "pseudonitrosites" (**48**) and  $\alpha$ -nitroketone oximes (**49**) can be



<sup>271</sup> M. O. Forster, *J. Chem. Soc.* **83**, 514 (1903).

<sup>272</sup> C. R. Kinney and H. J. Harwood, *J. Am. Chem. Soc.*, **49**, 514 (1927).

<sup>273</sup> A. Angeli, *Ber. Dtsch. Chem. Ges.*, **24**, 3994 (1891).

<sup>274</sup> A. Angeli, *Ber. Dtsch. Chem. Ges.*, **25**, 1956 (1892).

<sup>275</sup> A. Angeli, *Gazz. Chim. Ital.* **22**(2), 325 (1892).

<sup>276</sup> A. Angeli, *Gazz. Chim. Ital.* **22**(2), 445 (1892).

<sup>277</sup> A. Angeli and P. Bartolotti, *Gazz. Chim. Ital.* **22**(2), 493 (1892).

<sup>278</sup> C. Boeris, *Gazz. Chim. Ital.*, **23**(2), 165 (1893).



identified. Whether the nitro group of **49** supplies one or both of the oxygen atoms of the cyclization product (**50**) is not known, but, from the specificity of the reaction, it seems that a symmetrical intermediate, e.g., **51**, which could be envisaged as being formed by electrocyclization of the *aci*-nitroxime, is not involved. The configuration of the oxime group of the intermediate **49** is also unknown.

Other olefins are amenable to this method, using dinitrogen trioxide for pseudonitrosite formation.<sup>279-285</sup> The sulfur trioxide-dimethyl formamide complex has been found convenient for dehydrating some alicyclic  $\alpha$ -nitroximes.<sup>285</sup> According to various reports, the pseudonitrosites are converted into furoxans on heating in alcohol or water<sup>18,19,273-277</sup> and  $\alpha$ -nitroximes or their salts give the furoxans with acids.<sup>279-284</sup>

Sometimes nitrofuroxans are produced. The explosive 3-methyl-4-nitro compound (**52**) is formed from propene and dinitrogen trioxide or tetroxide when no oxygen is added to the reaction,<sup>286,287</sup> and also by the action of nitrous acid on methacrylic acid.<sup>127</sup> 4-Nitro-3-phenylfuroxan is a by-product of the reaction of nitrogen oxides (from nitric acid and arsenious oxide) and cinnamaldehyde.<sup>288</sup>

#### D. MISCELLANEOUS FUROXAN SYNTHESSES

In an interesting, and tidier, variant of the reactions in Section IV.C,  $\alpha$ -nitroketones of the sugar series are prepared from  $\alpha$ -tosyloxyketones as outlined in Scheme 2, and converted into furoxans by heating.<sup>289</sup>

Azidonitroolefins may be generated in a variety of ways, and they spontaneously decompose to furoxans, with loss of nitrogen. Thus, nitration ( $\text{NO}_2\text{BF}_4$ ) of a 1,2-dialkylvinyl azide,<sup>290</sup> treatment of a 1,2-dinitroolefin

<sup>279</sup> P. M. D. Klamann, W. W. Koser, P. Weyerstahl, and M. Fligge, *Chem. Ber.* **98**, 1831 (1965).

<sup>280</sup> P. M. D. Klamann and W. W. Koser, German Patent 1,257,150 (1967) [*CA* **69**, 10442 (1968) (errors in abstract)].

<sup>281</sup> H. Inoue, *Yakugaku Zasshi* **87**, 1419 (1967) [*CA* **69**, 18760 (1968)].

<sup>282</sup> V. Bruckner and E. Vinkler, *J. Prakt. Chem.* [2] **142**, 277 (1935).

<sup>283</sup> A. Lang, Ger. Offen. 2,062,928 (1971) [*CA* **75**, 110690 (1971)].

<sup>284</sup> H. Diefenbach and K. L. Platt, German Patent 2,534,400 (1977) [*CA* **86**, 141744 (1977)].

<sup>285</sup> J. Crosby, R. M. Paton, and R. A. C. Rennie, German Patent 2,424,700 (1974) [*CA* **84**, 44067 (1976)]; British Patent 1,474,693 (1977) [*CA* **87**, 201545 (1977)].

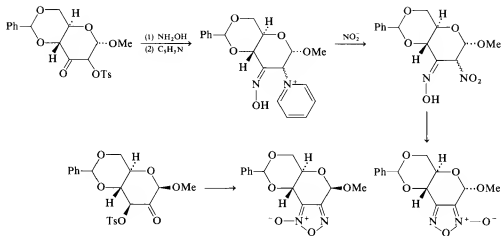
<sup>286</sup> N. Levy and C. W. Scaife, *J. Chem. Soc.*, 1100 (1946).

<sup>287</sup> S. Fumasoni, G. Giacobbe, R. Martinelli, and G. Schippa, *Chim. Ind. (Milan)* **47**, 1064 (1965).

<sup>288</sup> H. Wieland, *Justus Liebigs Ann. Chem.* **328**, 154 (1903).

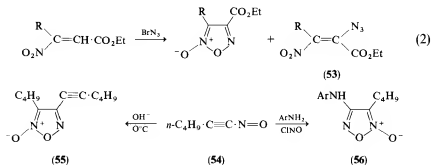
<sup>289</sup> C. S. Wu, W. A. Szarek, and J. K. N. Jones, *J. C. S. Chem. Commun.*, 1117 (1972).

<sup>290</sup> A. N. Thakore, J. Buchshriber, and A. C. Oehlschlager, *Can. J. Chem.* **51**, 2406 (1973).



SCHEME 2

with azide ion,<sup>291</sup> and reaction of 2-nitroacrylic esters with bromine azide,<sup>292</sup> all produce furoxans; the last is reported also to form the *trans*-nitroazide (53) (Eq. 2).



Furoxans have appeared rather unexpectedly in two nitrosoacetylene reactions. Base induces dimerization of 1-nitroso-1-hexyne (54), giving butyl-hexynylfuroxan (55, or its isomer).<sup>293</sup> With anilines, and in the presence of nitrosyl chloride used in its preparation, the nitroso compound 54 formed arylaminofuroxans (56).<sup>294</sup> The structure of one of these (56;  $\text{Ar} = p\text{-BrC}_6\text{H}_4$ ) was proved by X-ray crystallography.<sup>53</sup>

<sup>291</sup> W. D. Emmons and J. P. Freeman, *J. Org. Chem.* **22**, 456 (1957).

<sup>292</sup> C. Shin, Y. Yonezawa, K. Suzuki, and J. Yoshimura, *Bull. Chem. Soc. Jpn.* **51**, 2614 (1978) [*CA* **89**, 214861 (1978)].

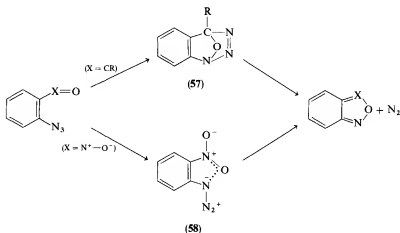
<sup>293</sup> E. Robson, J. M. Tedder, and D. J. Woodcock, *J. Chem. Soc. C*, 1324 (1968).

<sup>294</sup> J. M. Tedder and D. J. Woodcock, *J. Chem. Res. (S)*, 356 (1978).

## E. BENZOFUROXANS AND OTHER AROMATIC-RING-FUSED SYSTEMS

The previous review in this series<sup>6</sup> summarized the synthetic routes to fused furoxans up to 1968, and, despite the very considerable development in the applications of benzofuroxans since that time, the standard methods for their preparation are still applied, and no original synthesis has been developed.

The pyrolysis of *o*-nitrophenyl azides is perhaps the most reliable general method, the azides being available by a variety of routes. The pyrolysis temperature is usually considerably lower than is necessary to decompose *m*- or *p*-nitrophenyl azides, and the nitro group is generally agreed to take part in the displacement of the nitrogen.<sup>295</sup> The mechanism of this and similar reactions has been the subject of some discussion. There is a close parallel between nitroazide pyrolysis, forming benzofuroxans, and the generation of anthranils from *o*-azidoaryl ketones.<sup>296</sup> According to Hall *et al.*,<sup>297</sup> the ketones undergo an intramolecular cycloaddition of the azide group to the adjacent C=O function, to form an intermediate (57) which loses nitrogen. An analogous intermediate in the *o*-nitroazide reaction was



SCHEME 3

considered less likely, and a simple concerted cyclization and elimination (58)<sup>295</sup> was favored (Scheme 3). More recently, Dyall has produced argu-

<sup>295</sup> L. K. Dyall and J. E. Kemp, *J. Chem. Soc. B*, 976 (1968).

<sup>296</sup> R. K. Smalley, *Adv. Heterocycl. Chem.* **29**, 1 (1981).

<sup>297</sup> J. H. Hall, F. E. Behr, and R. L. Reed, *J. Am. Chem. Soc.* **94**, 4952 (1972).

ments, based on steric effects of ortho substituents, challenging the notion of **57** as an intermediate in these and other azide decompositions.<sup>298,299</sup>

The azide pyrolysis route has been used in the preparation of a wide variety of substituted benzofuroxans by Ghosh and Whitehouse,<sup>300</sup> and it has been extensively applied to the synthesis of specific examples, for instance, the 5-carboxylic acid,<sup>301,302</sup> the 4-chloro-5-methyl compound,<sup>303</sup> and others.<sup>304</sup> It has been used to prepare heterocyclic-fused furoxans such as thieno[2,3-*c*]furoxan,<sup>102,305</sup> some pyrido-,<sup>103,306</sup> quinolino-,<sup>100</sup> pyrimido-,<sup>106,307</sup> and pyridazino-<sup>308</sup> furoxans, and oxadiazolo-,<sup>101,309</sup> imidazo-,<sup>310</sup> and thiadiazolo-<sup>309,311</sup> benzofuroxans. When the azido or nitro group is severely ortho-crowded,<sup>298,300,312</sup> or when the azide group has to be disengaged from fusion into a tetrazole ring,<sup>104,106,306,307</sup> more forcing conditions are sometimes needed, and other methods may be found superior.<sup>104</sup> On the other hand, some *o*-nitroazides are so labile that it is not practicable to attempt to isolate them.<sup>101,308,309,313</sup> Although generally reliable, the method has occasionally been reported to fail, or prove markedly inferior to others.<sup>300,314</sup> 2-Azido-3-nitronaphthalene formed none of the linearly fused naphtho[2,3-*c*]furoxan, which so far has eluded synthesis.<sup>100,315</sup> Photolysis is an alternative to thermolysis,<sup>301</sup> as was known at the time of the earlier reviews.<sup>4,312</sup>

Oxidation of *o*-nitroanilines (**59**) is another widely applied route to benzofuroxans. Alkaline hypochlorite is commonly used, and in this case the *N*-chloronitroanilide anion (**61**) is a probable intermediate (Eq. 3). The

<sup>298</sup> L. K. Dyal, *Aust. J. Chem.* **28**, 2147 (1975).

<sup>299</sup> L. K. Dyal, *Aust. J. Chem.* **30**, 2669 (1977).

<sup>300</sup> P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.* **11**, 305 (1968).

<sup>301</sup> T. Nishikubo and T. Takaoka, *Nippon Kagaku Kaishi*, 327 (1975) [*CA* **82**, 156762 (1975)].

<sup>302</sup> T. Nishikubo, Japanese Patent 76/04,982 (1976) [*CA* **85**, 160104 (1976)].

<sup>303</sup> A. S. Angeloni, D. Dal Monte, E. Sandri, and G. Scapini, *Tetrahedron* **30**, 3849 (1974).

<sup>304</sup> P. Grieco and J. P. Mason, *J. Chem. Eng. Data* **12**, 623 (1967).

<sup>305</sup> C. Paulmier, G. Ah-Kow, and P. Pastour, *Bull. Soc. Chim. Fr.*, 1437 (1975).

<sup>306</sup> J. H. Boyer, D. I. McCane, W. J. McCarville, and A. T. Tweedie, *J. Am. Chem. Soc.* **75**, 5298 (1953).

<sup>307</sup> C. Temple, C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.* **33**, 2086 (1968).

<sup>308</sup> A. Karklina and E. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.*, 718 (1972) [*CA* **78**, 72037 (1973)]. The Abstract states that the furoxan was formed by the action of "NaNO<sub>3</sub>" on a chloro-nitropyridazinone; NaN<sub>3</sub> was probably the reagent used.]

<sup>309</sup> P. B. Ghosh and B. J. Everitt, *J. Med. Chem.* **17**, 203 (1974).

<sup>310</sup> R. C. Perera, R. K. Smalley, and L. G. Rogerson, *J. Chem. Soc. C*, 1348 (1971).

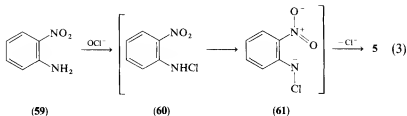
<sup>311</sup> P. B. Ghosh, *Tetrahedron Lett.*, 2999 (1971).

<sup>312</sup> A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.* **10**, 14 (1969).

<sup>313</sup> P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.* **12**, 505 (1969).

<sup>314</sup> P. Hadjimihalakis, *J. Heterocycl. Chem.* **13**, 1327 (1976).

<sup>315</sup> R. Selvarajan and J. H. Boyer, *J. Org. Chem.* **36**, 3464 (1971).



chloroanilines (**60**) can be prepared independently (with  $\text{Cl}_2\text{O}$  in  $\text{CCl}_4$  on the nitroaniline<sup>316</sup>), and they decompose to the furoxans in alkali, with transient generation of a deep red-purple color, which is usually seen in the course of the hypochlorite oxidation. The hypochlorite method is occasionally reported to succeed when the nitroazide pyrolysis fails, as with the *p*-dioxin-fused compound **62**.<sup>314</sup> However, the alkaline oxidizing conditions sometimes destroy the product, for instance, in the haloalkoxy-substitution reaction.<sup>317</sup> In these cases phenyliodosodiacetate, in benzene or toluene, may be effective<sup>102,318,319</sup>; it is recommended (but without experimental details) for the preparation of some pyridofuroxans from the appropriate 2-amino-3-nitropyridines.<sup>104</sup> The kinetics of the iodosodiacetate oxidation have been studied.<sup>319</sup>

The oxidation of *o*-quinone dioximes to benzofuroxans has been known since the early years,<sup>15</sup> and it is an efficient route, but not often a practical one, since the most convenient way to prepare an *o*-quinone dioxime is usually by reduction of the benzofuroxan (see Section V,D). Other methods—from *o*-quinones or *o*-nitrosophenols with hydroxylamine—are known: these were well established at the time of the earlier reviews, and the reaction needs no further mention here. Ferricyanide oxidation of the trioxime **63** gives the fused furoxan **64**.<sup>102</sup> Benzofuroxan appeared as a by-product in the reaction of *o*-benzoquinone dioxime with diselenium dichloride.<sup>320</sup>

Although *o*-nitrophenylhydroxylamines are at the right oxidation level for dehydration to benzofuroxans (cf.  $\alpha$ -nitroketoximes, Section IV,C), reports of this conversion are sporadic and on occasion incorrect.<sup>312,321–324</sup>

<sup>316</sup> K. J. Chapman and L. K. Dyll, *Aust. J. Chem.* **29**, 367 (1976).

<sup>317</sup> F. B. Mallory, C. S. Wood, and B. M. Hurwitz, *J. Org. Chem.* **29**, 2605 (1964).

<sup>318</sup> L. K. Dyll and K. H. Pausacker, *Aust. J. Chem.* **11**, 491 (1958).

<sup>319</sup> L. K. Dyll and J. E. Kemp, *Aust. J. Chem.* **26**, 1969 (1973).

<sup>320</sup> C. L. Pedersen, *Acta Chem. Scand.* **30B**, 675 (1976); *J. C. S. Chem. Commun.*, 704 (1974).

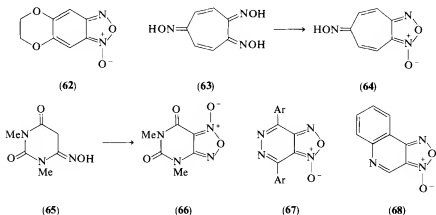
<sup>321</sup> M. Giua, *Gazz. Chim. Ital.* **53**, 657 (1923).

<sup>322</sup> A. S. Bailey, M. Maung, G. W. F. Orpwood, and J. E. White, *Tetrahedron* **22**, 995 (1966).

<sup>323</sup> M. Maung, *Union Burma J. Sci. Technol.* **1**, 207 (1968) [*CA* **71**, 101786 (1969)].

<sup>324</sup> M. Hasegawa, Y. Uchino, M. Satomi, and T. Okamoto, *Yakugaku Zasshi* **95**, 147 (1975) [*CA* **83**, 10766 (1975)].

The pyrimidine **65** forms the fused derivative **66** with nitric or nitrous acid.<sup>106,325,326</sup>



Fused furoxans can also be prepared by building an aromatic ring onto a preformed furoxan nucleus. Thus, hydrazine condenses with diacylfuroxans to give pyridazinofuroxans (**67**).<sup>178,188,327</sup>

Nitric oxide reacts with quinoline in acetic anhydride in a very curious way, to give a compound tentatively suggested to be the quinolinofuroxan **68**.<sup>328</sup> This identification is probably correct, since the reported melting point is only 2°C below that found for the same compound prepared by a more conventional method.<sup>100</sup>

4-Formylbenzofuroxans are formed by rearrangement of 7-nitroanthranils (see Section V,C,4).

## V. Ring Reactions

### A. CLEAVAGE TO NITRILE OXIDES

This reaction is the reverse of the dimerization described in Section IV,A. Early workers found that phenyl isocyanate could be produced on thermolysis of diphenylfuroxan,<sup>329</sup> and benzonitrile oxide was found to rearrange

<sup>325</sup> F. Yoneda, Y. Sakuma, and M. Ueno, *J. Heterocycl. Chem.* **10**, 415 (1973).

<sup>326</sup> F. Yoneda and Y. Sakuma, *J. Heterocycl. Chem.* **10**, 993 (1973).

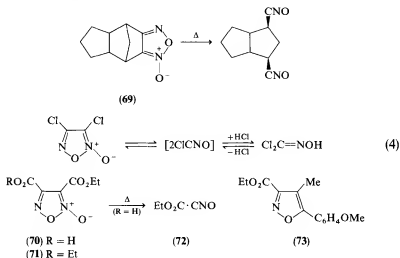
<sup>327</sup> O. Widman and E. Virgin, *Ber. Dtsch. Chem. Ges.* **42**, 2894 (1909).

<sup>328</sup> M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 944 (1957).

<sup>329</sup> S. Gabriel and M. Koppe, *Ber. Dtsch. Chem. Ges.* **19**, 1145 (1886); K. von Auwers and V. Meyer, *ibid.* **22**, 705 (1889).

to the isocyanate under similar conditions.<sup>150,156,330</sup> Later, certain strained furoxans (**13**, **69**) were found to ring-open under much milder conditions, and in the presence of dipolarophiles they formed isoxazole and isoxazoline adducts.<sup>61,97</sup> Bulky substituents were also found to facilitate ring cleavage: di(1-adamantyl)furoxan afforded 1-adamantylcarbonitrile oxide, which could be trapped with styrene or rearranged to the isocyanate.<sup>155</sup> The strained furoxans (e.g., **69**) have recently been investigated more fully, as a potential source of diisocyanates for polymer production,<sup>76</sup> since the rearrangement of the nitrile oxide to the isocyanate grouping (and also, to some extent, the opening of the furoxan ring<sup>76</sup>) is efficiently catalyzed by sulfur dioxide<sup>331</sup> and by  $\alpha$ -diketones.<sup>332</sup> Unstrained furoxans were also found to provide nitrile oxide adducts when vigorously heated in the presence of dipolarophiles.<sup>333</sup> Flash vacuum pyrolysis has also been applied, and under these conditions it was possible to prepare and isolate the reactive acetonitrile oxide from dimethylfuroxan.<sup>334</sup>

It seems that dichlorofuroxan is able to dissociate into chloroformonitrile oxide, at least in the presence of hydrogen chloride, since on heating the equilibrium of Eq. (4) was observed.<sup>227</sup> However, no other trapping experiments were performed.



<sup>330</sup> H. Wieland, *Ber. Dtsch. Chem. Ges.* **42**, 4207 (1909).

<sup>331</sup> E. H. Burk and D. D. Carlos, *J. Heterocycl. Chem.* **7**, 177 (1970).

<sup>332</sup> J. Crosby and J. A. Milner, German Patent 2,714,668 (1977) [*CA* **88**, 23601 (1977)].

<sup>333</sup> J. A. Chapman, J. Crosby, C. A. Cummings, R. A. C. Rennie, and R. M. Paton, *J. C. S. Chem. Commun.*, 240 (1976).

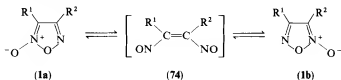
<sup>334</sup> W. R. Mitchell and R. M. Paton, *Tetrahedron Lett.*, 2443 (1979).

Other reactions which form nitrile oxides or their cycloadducts from furoxans are known, but in the majority of these cases their course is not clear. 4-Phenylfuroxan with mild base rearranges to the isomeric  $\alpha$ -oximino-phenylacetonitrile oxide (see Section VI). The distillation of 3-ethoxycarbonylfuroxan-4-carboxylic acid (**70**) appears to generate the nitrile oxide **72**, since one of the products isolated is diethyl furoxandicarboxylate (**71**).<sup>335,336</sup> The diester (**71**) with anethole is reported to form ethyl 4-anisyl-5-methylisoxazole-3-carboxylate (**73**),<sup>337</sup> but it is not established that the reaction involves the generation of **72** by dissociation of **71**, as the authors suggested (see Section V,C,1). See also Section X.

## B. THERMAL AND PHOTOCHEMICAL ISOMERIZATION

### 1. General Discussion

The interconversion of two isomeric furoxans (**1a**  $\rightleftharpoons$  **1b**;  $R^1 \neq R^2$ ) is one of the most important and characteristic features of the chemistry of these compounds. The existence of this equilibrium was first discovered by Ponzio,<sup>23,25</sup> who erroneously considered it to be the interconversion of furoxan (**1**) and dioxadiazine (**2**) structures. Auwers was probably the first to ascribe the equilibrium to furoxan interconversion (**1a**  $\rightleftharpoons$  **1b**), suggesting that an intermediate of type **4** was involved.<sup>140</sup> The rate of the reaction is very strongly dependent upon the presence or absence of aromatic ring fusion to the furoxan bond *c*. Reference has already been made to this in Section II,A because the isomerism and the isomerization were both sources of much mystification to early chemists.



It seems reasonable to assume a dinitrosoethylene structure (**74**) (or dinitrosobenzene, for the benzofuroxans) as intermediate. This was originally suggested by Hammick *et al.*<sup>34</sup> and supported by Mallory *et al.*<sup>31,99</sup> from bond energy arguments, and also by consideration of the entropy of activation. This was found to be small, but positive in sign, perhaps indicating a

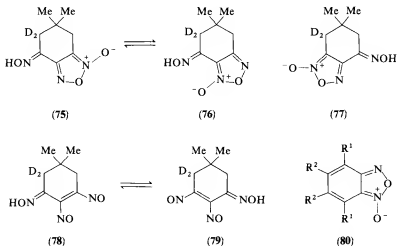
<sup>335</sup> M. M. Bouveault and A. Bongert, *Bull. Soc. Chim. Fr.* [3] **27**, 1164 (1902).

<sup>336</sup> C. Grundmann, *Fortschr. Chem. Forsch.* **7**, 62 (1966).

<sup>337</sup> M. Sakamoto, M. Shibano, and Y. Tomimatsu, *J. Pharm. Soc. Jpn.* **93**, 1643 (1973).



tendency to increasing disorder as the transition state is reached. No evidence, however, has yet been found for a true intermediate dinitroso compound, even in the benzofuroxans, and Calzaferri *et al.*<sup>339</sup> were unable to locate an energy minimum corresponding to such a species in their calculations on the benzofuroxan isomerization. Nevertheless, an appreciable entropy contribution to the stabilization of the intermediate could give rise to a real energy minimum, even if enthalpy calculations are correct in their failure to reveal one. In the case of benzofuroxan, thermochromism attributed to the presence of *o*-dinitrosobenzene has been reported,<sup>34</sup> but this has not been investigated further. *o*-Dinitrosobenzenes are also suggested as intermediates in some benzofuroxan reactions.<sup>338,339</sup> However, this evidence must be regarded as speculative: alternative mechanisms can be devised which avoid the necessity for opening the ring before the reaction occurs, and other reagents, e.g. dienes,<sup>340</sup> which normally react with nitroso groups, fail to do so with benzofuroxans (see Sections V,C,3 and VIII). The deuterated oxime **75** rearranges to **76** without any appreciable further ring interconversion (to form **77**).<sup>341</sup> It was argued that this is evidence against the existence of a dinitroso intermediate (**78**) of more than transitory lifetime, since proton transfer (and bond rotation) in **78** is (are) all that is needed to form **79**, the rearrangement intermediate of the isomeric oxime **77**.<sup>342</sup>



<sup>338</sup> E. Abushanab and N. D. Alteri, *J. Org. Chem.*, **40**, 157 (1975).

<sup>339</sup> A. B. Bulacinski, E. F. V. Scriven, and H. Suschitzky, *Tetrahedron Lett.*, 3577 (1975).

<sup>340</sup> G. Kresze and H. Bathelt, *Tetrahedron* **29**, 1043 (1973).

<sup>341</sup> J. Ackrell, Ph.D. Thesis, University of East Anglia (1973).

<sup>342</sup> A. J. Boulton, *Lect. Heterocycl. Chem.*, **2**, 45 (1974).

2. *Equilibration Rates*

In this section we consider first the unfused furoxans, then those fused to nonaromatic rings, and finally those fused to aromatic systems. The three classes show progressively increasing isomerization rates, although there is really no clear dividing line between the second and third groups.

The first careful rate measurements on the interconversion of unfused furoxans were made by Mallory and Cammarata,<sup>31</sup> who studied the 4-ethyl-3-methyl and 3-methyl-4-phenyl compounds (**1a**;  $R^1 = \text{Me}$ ,  $R^2 = \text{Et, Ph}$ ), and we<sup>79</sup> obtained further data for five other methyl furoxans. The activation parameters are given in Table V. Much earlier, Milone<sup>343</sup> had made some rate studies on similar compounds (considered, following Ponzio, to be interconversions of ring systems **1**  $\rightleftharpoons$  **2**), but the figures he obtained are not reliable.

TABLE V  
ACTIVATION PARAMETERS<sup>a</sup> FOR THE INTERCONVERSION OF FUROXANS

No.	Formula	$R^1$	$R^2$	$T$ (°C)	$\Delta G^\ddagger$	$\Delta H^\ddagger$	$\Delta S^\ddagger$	Ref.
1	<b>1a</b>	Me	Et	100	134	147	34	31
2	<b>1a</b>	Me	Ph	100	133	140	16	31
3	<b>1a</b>	Me	CO <sub>2</sub> Et	100	134	146	32	79
4	<b>1a</b>	Me	COCl	100	135	148	36	79
5	<b>1a</b>	Me	SO <sub>2</sub> Ph	100	131	132	5	79
6	<b>1a</b>	Me	SPh	100	122	129	18	79
7	<b>1b</b>	Me	NHCO <sub>2</sub> CH <sub>2</sub> Ph	100	116	125	27	79
8	<b>5</b>			25	58.4	64.8	21	90
9	<b>80</b>	H	Cl	30	55.2	60.2	25	99
10	<b>80</b>	Cl	H	30	60.6	66.5	21	99
11	<b>10</b>			25	88	92	13	72
12	<b>11</b>			25	82	88	19	72

<sup>a</sup> Heats are expressed in kJ mol<sup>-1</sup>, entropies in J K<sup>-1</sup> mol<sup>-1</sup>. The errors estimated for  $\Delta G^\ddagger$  and  $\Delta H^\ddagger$  were all ~3–4% of the figures quoted; errors in  $\Delta S^\ddagger$  ranged from 3 to 10 J K<sup>-1</sup> mol<sup>-1</sup>.

<sup>b</sup> At temperature  $T$ .

Energy barriers appear to be significantly lower when an electron-donor substituent is present (Table V, entries 6 and 7); other qualitative data confirm this.<sup>79,86</sup> Although these cases are of heavily biased equilibria, the barrier is somewhat lower even when approached from the stabler side.

Fusion to an aliphatic six-membered ring produces a small acceleration in the isomerization rate.<sup>80</sup> This can reasonably be attributed to strain

<sup>343</sup> M. Milone, *Gazz. Chim. Ital.* **59**, 829 (1929).

effects (see discussion in Ref. 102). Five-membered ring fusion might be expected to result in a still more rapid rearrangement; such systems are, however, susceptible to the cleavage of both C—C and N—O bonds (Section V,A), and no rates have been measured for these compounds.

When an aromatic ring is fused to bond *c* of the furoxan, there is a dramatic decrease in the energy barrier (Table V, entries 8–12). Again, it was Mallory *et al.*<sup>99</sup> who made the first reliable measurements, from line-shape data from the <sup>1</sup>H-NMR spectra (see Section III,C). Other line-shape studies have been reported for benzofuroxan<sup>90</sup> and for 5-halobenzofuroxans.<sup>38,91</sup> The results from the halo derivatives deserve comment. Although “coalescence temperatures” were very similar for all the compounds, the quoted Arrhenius parameters were widely divergent (even for the same compound measured at different spectrometer frequencies<sup>91</sup>);  $\Delta S^\ddagger$  values ranged from  $-140$  (for 5-fluoro-) to  $+140 \text{ J K}^{-1} \text{ mol}^{-1}$  (for 5-iodobenzofuroxan).<sup>38</sup> We consider that these results are not reliable, and that they do not justify the authors’ conclusion (supported though it is by bond energy calculations) that the transition state of the reaction is the “ $\psi$ -*o*-dinitrosobenzene” (6), with linear nitroso groups.

Direct (as opposed to DNMR) rate measurement methods have also been applied to benzofuroxans. Calzaferri *et al.*<sup>39</sup> disturbed the equilibria of some 4-substituted benzofuroxans photochemically and measured the rate constants for the reversion of the unstable to the stable tautomers by UV spectrophotometry (see Section V,B,4). The results were in generally good agreement with those obtained by the DNMR method. (The compounds studied were not the same; the DNMR method is best applied to equilibria which are fairly evenly balanced, while for the photochromism rate studies heavily biased examples are appropriate.)

Isomerization rates of 4,7-dichloro- and -dibromobenzofuroxan are significantly lower than those for the 5,6-dichloro compound<sup>99</sup> (Table V, entries 9 and 10). This was attributed to steric effects in the 4,7-disubstituted compounds, the N<sub>2</sub>O<sub>2</sub> group occupying a larger effective volume in the transition state than when the furoxan ring is closed. However, the value of this evidence in clarifying the nature of the transition state, and the question of the existence of a dinitroso intermediate, is uncertain. The authors were not able to obtain results for the corresponding 4,7- and 5,6-dimethyl compounds.

Approximate barrier heights, from coalescence temperature measurements, are available for a number of substituted benzofuroxans.<sup>103–105</sup> The effect of the substituents is not noticeable, variations being within the range of accuracy of the measurements. Aza substitution, in the pyridofuroxans 14, 81, and 82,<sup>104</sup> and in the pyrimidofuroxan 15,<sup>106</sup> results in heavily biased

equilibria, and only very rough estimates of the barrier heights have been made; they seem to be similar to those in the benzofuroxans.



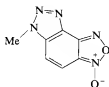
(81) R = H, Me



(82)

(83) X = N  
(84) X = N<sup>+</sup>—O<sup>-</sup>

(85)



(86)



(87)

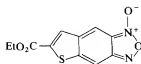
The effect of fusion of another ring to benzofuroxan is rather variable. Naphtho[1,2-*c*]furoxan (**16**) and some of its derivatives show  $\Delta G^\ddagger \approx 83 \text{ kJ mol}^{-1}$ .<sup>100</sup> Accurate data are available for two fused benzofuroxans, **10** and **11** (see Table V),<sup>72</sup> and qualitative  $T_c$  measurements have been made on a number of related compounds.<sup>100,101,344,345</sup> The slowest interconversions were noted for the furoxano- and furazano-fused compounds (**83**, **84**).<sup>101</sup> The (heavily biased) isomeric *N*-methyltriazole derivatives **85** and **86** were, qualitatively, rather more rapidly isomerized than were compounds **10** or **16**,<sup>344</sup> while the fused thiadiazole **87**<sup>344</sup> ( $\Delta G^\ddagger 72 \text{ kJ mol}^{-1}$ ), thiophene **88**<sup>345</sup> (69 kJ), and thiazole **89**<sup>344</sup> (64 kJ mol<sup>-1</sup>) had still lower barriers. The fastest furoxan yet to be measured is the "linear-fused" example **90** ( $\Delta G^\ddagger$



(88)



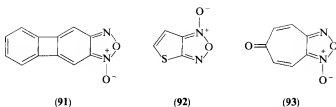
(89)



(90)

<sup>344</sup> R. C. Brown, Ph.D. Thesis, University of East Anglia (1970).

<sup>345</sup> D. Middleton, Ph.D. Thesis, University of East Anglia (1974).



48 kJ mol<sup>-1</sup>).<sup>345</sup> Another 5,6-fused benzofuroxan is the biphenylene derivative **91**, but here, as might be expected from the preferred  $\pi$ -bond arrangement in the parent hydrocarbon, the (degenerate) interconversion is rather slow ( $\Delta G^\ddagger$  86 kJ mol<sup>-1</sup>).<sup>102</sup>

In an attempt to gauge "aromaticity" of some nonbenzenoid rings by measuring the isomerization energy barriers of their fused furoxan derivatives, the thienofuroxan **92** and the troponofuroxan **93** were prepared. The former showed a remarkably rapid equilibration ( $\Delta G^\ddagger$  56 kJ mol<sup>-1</sup>); the latter was too slow ( $\Delta G^\ddagger > 100$  kJ) to be measured by DNMR methods.<sup>102</sup> The authors concluded that ring strain plays an important role in accelerating the equilibration of the thiophene derivative.

### 3. Equilibrium Constants

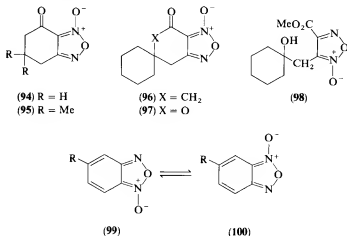
It is apparent that the equilibrium constants for the furoxan isomerizations are determined by a combination of factors, not all fully understood, and of varying importance, depending on the substituents and the way in which they are able to interact with the two positions of the heterocyclic ring. Equilibria are conveniently measured by <sup>1</sup>H NMR, at low temperatures for the benzofuroxans and other rapidly exchanging systems, or at normal temperatures for the slowly equilibrating types. The assignments of the spectra are made using the criteria outlined in Section III.C.

Electron-releasing substituents consistently favor the 4-position in the monocyclic series. Thus, in the aminoarylfuroxans (**8**  $\rightleftharpoons$  **9**) the 3-amino forms (**9**) are undetectable at equilibrium,<sup>86</sup> and phenoxy and pyrrolidino substituents show a similar strong preference for the 4-position.<sup>79</sup> A phenylthio group is less selective, **1b** ( $R^1 = \text{PhS}$ ,  $R^2 = \text{Me}$ ) being only  $\sim 1$  kJ mol<sup>-1</sup> more stable than the isomer **1a**.<sup>79</sup> A corresponding preference for electron-accepting substituents to favor the 3-position is, in general, *not* observed. Although the ketones **94–96**,<sup>80,346</sup> the lactone **97**,<sup>347</sup> and some related compounds are more stable than their isomers by some 6–9 kJ mol<sup>-1</sup>, methanolysis of **97** forms an ester which is less stable than its isomer (**98**) by

<sup>346</sup> S. H. Imam, M.Sc. Thesis, University of East Anglia (1973).

<sup>347</sup> J. S. Khosrowshahi, M.Sc. Thesis, University of East Anglia (1977).

$\sim 2 \text{ kJ mol}^{-1}$ .<sup>347</sup> A number of derivatives of 3-methylfuroxan-4-carboxylic acid (**1a**;  $R^1 = \text{Me}$ ,  $R^2 = \text{CO}_2\text{H}$ ) (the acid itself is too unstable to be isomerized without decomposition) are favored over the corresponding isomers (**1b**), unless form **1b** can be stabilized by hydrogen bonding.<sup>79</sup> and the 4-acetyl-3-methyl compound (**1a**;  $R^1 = \text{Me}$ ,  $R^2 = \text{COMe}$ ) is also preferred ( $\sim 0.8 \text{ kJ mol}^{-1}$ ) over its isomeric form.<sup>348</sup> A few data are available on dialkyl-<sup>31</sup> and alkylarylfuroxan<sup>31,85</sup> equilibria; free energy differences are small and apparently determined by steric effects. Measurements on the equilibrium of the two monophenylfuroxans (**17**  $\rightleftharpoons$  **18**) are complicated by the simultaneous decomposition of the 4-phenyl isomer (**17**): qualitatively, there is a small preference for this isomer (at  $130^\circ\text{C}$ , in  $\text{Cl}_3\text{C}\cdot\text{CH}_2\text{Cl}$ ).<sup>107</sup>



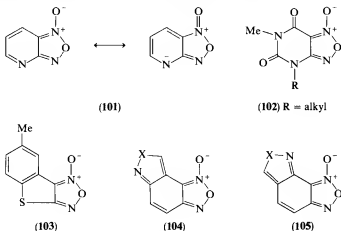
By comparison with the compounds with the substituents directly attached to the furoxan ring, 5(6)-substituted benzofuroxan (**99**  $\rightleftharpoons$  **100**) equilibria should be subject to attenuated electronic effects, and the steric effects should be removed. In these compounds, electron-acceptor substituents show the greatest consistency in behavior, with nitro,<sup>98</sup> carboxy,<sup>103</sup> carbethoxy,<sup>103</sup> and cyano<sup>344</sup> substituents favoring tautomers **100** by factors of up to 3:1 ( $\Delta G^\circ \leq 2 \text{ kJ mol}^{-1}$ ). Halo,<sup>38,91,103</sup> methoxy,<sup>103</sup> acetoxy,<sup>103</sup> methyl,<sup>103,104</sup> and morpholino<sup>349</sup> substitutions lead to small preferences for form **99**, but there is no clear correlation with the electron-donor properties of the group, and the acetamido compound ( $R = \text{NHCOMe}$ ) favors both tautomers equally.<sup>103</sup> The steric effect of a 4-methyl group produces an  $\sim 2\text{-kJ}$  bias directing the oxygen away from the group,<sup>104</sup> while 4-nitrobenzofuroxan

<sup>348</sup> M. Valmacco, Dipl. Pharm. Thesis, University of Turin (1978).

<sup>349</sup> S. Mzengeza, M.Sc. Thesis, University of East Anglia (1980).

shows no sign of its 7-nitro isomer, at equilibrium.<sup>39,98</sup> Some 4,7-disubstituted benzofuroxans have also been studied.<sup>105</sup>

Direct fusion of the furoxan to a heterocyclic ring usually leads to heavily biased equilibria. The thienofuroxan (**92**)<sup>102</sup> and the pyridofuroxans (**14**, **81**, **82**)<sup>104</sup> all predominate in the forms shown, to the extent of  $\sim 4 \text{ kJ mol}^{-1}$  in free energy. Although superficially similar, it seems likely that the former is a case of favored electron-donor conjugation to the 4-position, while in the pyridines electron-acceptor conjugation favors the 3-position (of the furoxan ring). It was suggested that the stabilizing effect of simple conjugation (**101**) was augmented by destabilization by dipolar repulsion in the alternative tautomer, to account for the heavy bias of the equilibrium,<sup>104</sup> and this is consistent with the result from the quinolinofuroxan **68**, where the nitrogen has a much smaller effect ( $\sim 2.8 \text{ kJ mol}^{-1}$ ).<sup>100</sup> The equilibria of the pyrimidine derivatives **102**<sup>106</sup> and the benzothiophene **103**<sup>341</sup> contain undetectably (by NMR) small amounts of the alternative tautomers.



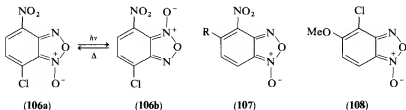
Equilibrium constants have been measured for the fused benzofuroxans mentioned in the previous subsection. That for the triazolo-fused compound (**11**) was found to be temperature-dependent, favoring the "O-outside" form, as shown, by factors of 2–3:1 ( $\Delta G^\circ 3.1 \pm 0.6 \text{ kJ mol}^{-1}$ ;  $\Delta S^\circ 4.7 \pm 1.3 \text{ J K}^{-1} \text{ mol}^{-1}$ ).<sup>72</sup> The isomeric triazolo-fused derivatives (**85**, **86**) have still larger O-outside preferences,<sup>344</sup> but the other equilibria are more evenly balanced, in some cases [e.g., **16**,<sup>100</sup> **87**, **104** ( $X = \text{O}$  and  $\text{S}$ ), and **105** ( $X = \text{S}$ ),<sup>344</sup> and the 4- and 5-chloro derivatives of **8**<sup>350</sup>] preferring O-inside forms, which is that found in **10** in the crystal,<sup>70</sup> although it is not (by a small factor) the predominant form in solution.<sup>72</sup>

<sup>350</sup> A. J. Boulton, A. C. G. Gray, and A. R. Katritzky, *J. Chem. Soc. B*, 909 (1967).

#### 4. Photochemical Isomerization

The above discussion has been concerned almost exclusively with the thermal isomerization; however, it is also possible to bring about the rearrangement **1a**  $\rightleftharpoons$  **1b** by light. Gagneux and Meier<sup>351</sup> found that the two aminophenylfuroxans (**8**, **9**; R = H), when irradiated with 254-nm light in diethyl ether, set up a photoequilibrium containing approximately equal proportions of each isomer. By irradiation with light > 300 nm, the 3-amino isomer was completely converted into the 4-amino compound (as in the thermal reaction). They also observed photoequilibration of the two methylphenyl isomers.<sup>351</sup> By the action of the full arc of a medium-pressure mercury discharge on 3-methyl-4-phenylsulfonylfuroxan in dichloromethane, a mixture of the two isomers was obtained in which the 4-methyl derivative predominated.<sup>352</sup> Other examples have been reported.<sup>79</sup>

The photoisomerization of benzofuroxans has also been investigated. The systems return very rapidly to their thermal equilibrium positions, but at low temperatures UV and NMR spectra of the unstable tautomer **106b** could be measured. The photoisomerization of **107** (R = H and Cl) and **108** was also studied, and the rates of reversion of their unstable forms were determined.<sup>39</sup>



### C. RING TRANSFORMATIONS

#### 1. Furoxans into Isoxazoles and Isoxazolines

4-Aryl-3-methylfuroxans (**109**) are converted into 3-arylisoxazolin-4-one oximes (**110**) by the action of alcoholic alkali hydroxides or alkoxides. This reaction, discovered but not fully understood by Tönnies,<sup>16</sup> was studied by Angeli *et al.*,<sup>273-278,353</sup> who proposed the structure **110** for the product,

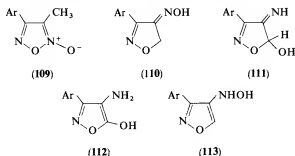
<sup>351</sup> A. R. Gagneux and R. Meier, *Lect., Int. Congr. Heterocycl. Chem.*, 2nd, 1969.

<sup>352</sup> R. Calvino, V. Mortarini, A. Gasco, M. A. Bianco, and M. L. Ricciardi, *Eur. J. Med. Chem.-Chim. Ther.* **12**, 157 (1977).

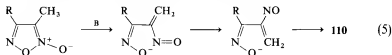
<sup>353</sup> G. Malagnini, *Gazz. Chim. Ital.* **24** (2), 1 (1894).



and by Wieland and Semper.<sup>19</sup> Ponzio and co-workers<sup>24,354,355</sup> made considerable use of the reaction for the removal of 4-aryl-3-methylfuroxans from their 3-aryl-4-methyl isomers. However, they also investigated the chemistry of the product, and on the basis of some faulty reasoning structure **111** was proposed in place of **110**. Earlier reviewers, in discussing this reaction, have either given Angeli's structure (**110**) and ignored Ponzio's reassignment,<sup>356</sup> or presented **111** or **112** without reference to **110**.<sup>357</sup>



This reaction, which has been known as the isoxazolinic transposition, or Angeli's rearrangement, has recently been reinvestigated, and Angeli's original formula (**110**) was found to be correct.<sup>358</sup> A full account of the chemistry of **110** would be beyond the scope of this review, but the main source of the confusion was the unsuspected tautomerism of **110** to the hydroxylamine **113**, to which Ponzio assigned structure **112**. The 4-benzyl-3-methylfuroxan rearranges in the same way,<sup>355,358</sup> but the 3,4-dimethyl compound appears to decompose more extensively in strongly basic media.<sup>359</sup> The mechanism outlined in Eq. (5) seems likely.



Reactions which generate nitrile oxides can lead to isoxazoles and isoxazolines by cycloaddition to acetylenes and olefins, respectively. The cleavage of the furoxan ring into two nitrile oxide molecules (or to a bis-nitrile oxide, in the case of a fused furoxan) is described in Section IV.A,

<sup>354</sup> G. Ponzio and M. Torres, *Gazz. Chim. Ital.* **59**, 461 (1929).

<sup>355</sup> F. S. De Paolini and G. Armitano, *Gazz. Chim. Ital.* **63**, 917 (1933).

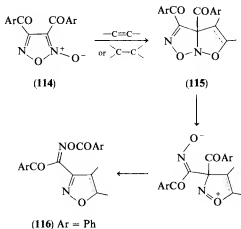
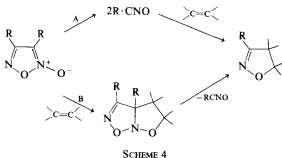
<sup>356</sup> J. V. R. Kaufman and J. P. Picard, *Chem. Rev.* **59**, 438 (1959); L. C. Behr, *Chem. Heterocycl. Compd.* **17**, 300 (1962).

<sup>357</sup> J. H. Boyer, *Heterocycl. Compd.* **7**, 490 (1961); R. A. Barnes, *ibid.* **5**, 481 (1957).

<sup>358</sup> A. J. Boulton, D. E. Coe, and P. G. Tsoungas, *Gazz. Chim. Ital.* **111**, in press (1981).

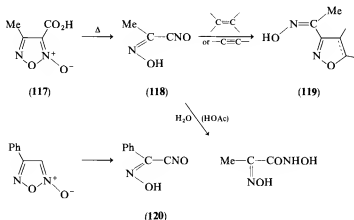
<sup>359</sup> A. N. Trethewey, University of East Anglia (unpublished work) (1980).

and cycloadducts have been reported from these (Scheme 4, path A).<sup>61,97,333,334</sup> In general, an alternative route (path B), via interaction of the dipolarophile with the furoxan prior to cleavage, is possible: there is no sound kinetic evidence either way. The isolation of the nitrile oxides by thermal decomposition in the absence of a dipolarophile makes path B an unnecessary hypothesis, but in some reactions of diacylfuroxans (**114**) such an interaction seems to be required. Dibenzoylfuroxan forms 1:1 adducts (**116**) with olefins and acetylenes; the route of Scheme 5 was proposed, formation of the intermediate **115** being followed by rearrangement, rather than loss of the nitrile oxide.<sup>360</sup> The dicarboxylic ester **71** is reported to form **73** with anethole.<sup>310</sup> Although the nitrile oxide **72** was suggested to be an intermediate in this case, the alternative mechanism (Scheme 4, path B) also seems possible here, since electron-withdrawing substituents have been found to enhance nitronc cycloaddition reactivity. (See Appendix.)



<sup>360</sup> M. Altaf-ur-Rahman, A. J. Boulton, and D. Middleton, *Tetrahedron Lett.*, 3469 (1972).

Decarboxylation and ring cleavage, followed by cycloaddition of the nitrile oxide **118**, probably account for the formation of adducts (**119**) from 4-methylfuroxan-3-carboxylic acid (**117**).<sup>361</sup> Analogously, 4-phenylfuroxan forms an adduct (or adducts) with mesityl oxide, apparently derived via the nitrile oxide **120**, which is produced from the furoxan under a variety of extremely mildly basic conditions.<sup>362</sup>



The early work on the formation of isoxazole derivatives by the action of primary amines on dibenzoylfuroxan has been summarized elsewhere.<sup>3-5</sup> The whole area is still a very complex and confused one, despite a number of more recent studies. Since most of the products of these reactions are now assigned pyrazole or furazan structures, the discussion is deferred to the following Section (V,C,2). Here we mention the isoxazole derivatives that are produced.

Aniline and dibenzoylfuroxan are reported to form the dark red 3-anilino-4-nitroso-5-phenylisoxazole (**121**; R = Ph) via an intermediate open-chain dioxime. Similar products (**121**; R = Me<sub>2</sub>CH, Me<sub>3</sub>C, H) have been obtained using primary amines<sup>363</sup> and ammonia<sup>364</sup> [this latter reaction had earlier been investigated by Ponzio and Cerrina,<sup>365</sup> who did not isolate **121** (R = Ph)]. Structure **121** (R = Ph) was first proposed by Wieland and Gmelin in 1910<sup>366</sup> and has stood the test of time (including a searching reinvestigation

<sup>361</sup> A. Gasco, V. Mortarini, R. Calvino, and A. Serafino, *Tetrahedron Lett.*, 627 (1974).

<sup>362</sup> J. V. Burakevich, R. S. Butler, and G. Volpp, *J. Org. Chem.* **37**, 593 (1972).

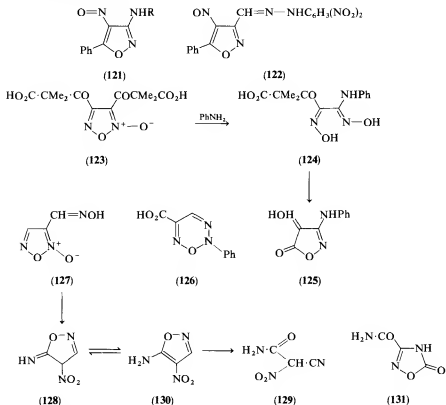
<sup>363</sup> A. V. Ereemeev, V. G. Andrianov, and I. P. Piskunova, *Khim. Geterotsikl. Soedin.*, 616 (1978) [*CA* **89**, 109270 (1978)].

<sup>364</sup> V. G. Andrianov and I. P. Piskunova, *Tezisy Dokl.—Resp. Konf. Molodykh Uch.-Khim.*, 2nd, 1977, 1, 43 (1977) [*CA* **89**, 109287 (1978)].

<sup>365</sup> G. Ponzio and C. Cerrina, *Gazz. Chim. Ital.* **58**, 26 (1928).

<sup>366</sup> H. Wieland and E. Gmelin, *Justus Liebigs Ann. Chem.* **375**, 297 (1910).

by Bertelson *et al.*<sup>367</sup>. Derivatives formerly considered as analogous (**121**; R = NHPh), also red in color, which are produced from dibenzoylfuroxan and phenylhydrazine,<sup>170</sup> have however been reassigned as pyrazole derivatives (see Section V.C.2). Other diacylfuroxans with phenylhydrazine form products to which nitrosoisoxazole structures of type **121** have been given<sup>87, 179, 181, 183</sup>; these also should be revised. A further related structure (**122**) has been reported from "Holleman's peroxide" (**29**) and dinitrophenylhydrazine.<sup>29</sup> A compound produced by the action of hydroxide ion on the aniline cleavage product (**124**) of the furoxan **123** was identified by Bertelson *et al.*<sup>367</sup> as the isoxazolinone **125**; this had previously been suggested to be an oxatriazine (**126**).<sup>368</sup>



The chemistry of the oligomers of fulminic acid is another area of great confusion in the literature, which was well summarized by Grundmann

<sup>367</sup> R. C. Bertelson, K. D. Glanz, and D. B. McQuain, *J. Heterocycl. Chem.* **6**, 317 (1969).

<sup>368</sup> W. H. Perkin, *J. Chem. Soc.* **83**, 1217 (1903).

and Grünanger<sup>369</sup> and by Behr<sup>370</sup> for the period prior to 1970. However, two subsequent papers, one dealing with the trimers ("fulminuric acids")<sup>371</sup> and one with the tetramers ("cyanilic acids"),<sup>372</sup> revised many accepted structures, and doubt still remains about others. Of relevance to the present section is the rearrangement of the oxime **127** to prefulminuric acid (**128**), brought about by brief exposure to mild base. Further rearrangement of **128** forms fulminuric acid (**129**).<sup>371</sup> There is still uncertainty over the configuration of the oxime group in **127**, and about the tautomeric structure of **128**, the spectra of which seem to favor the imine formula over **130**. Structure **128** was previously assigned to  $\gamma$ -fulminuric acid,<sup>373</sup> which is now shown to be **131**.<sup>371</sup>

## 2. *Furoxans into Furazans and Pyrazoles*

The simple deoxygenation of furoxans to furazans is covered in Section V.D.

The reactions of diacylfuroxans with ammonia, amines, and hydrazines have been the subject of much debate and controversy, and it seems to the reviewers that many areas still require clarification. The readily available dibenzoylfuroxan has been the substrate for most of the reactions. Some of these were investigated in 1961 by Bertelson *et al.*,<sup>367</sup> who surveyed the field and reassigned a number of structures.

The first identifiable product of the action of aniline on dibenzoylfuroxan is the open-chain amidoxime **133**.<sup>374</sup> This probably arises by attack of the aniline on the benzoyl group at C-3, elimination of benzanilide with ring opening, and addition of a further molecule of aniline to the nitrile oxide **132** (Scheme 6). Compound **133** is unstable, and readily cyclizes to the nitrosoisoxazole **134**.<sup>366</sup> It seems likely that aniline addition to **132** would initially form the *syn*-amidoxime, but isomerization to the *anti* isomer, with the required configuration for cyclization to **134**, could take place by prototropy and bond rotation, or simply by nitrogen inversion. The isoxazole **134** is itself unstable and undergoes an interesting rearrangement, spontaneously or on heating, to the colorless furazan **135** ( $R = Ph$ ).<sup>367,375</sup>

Russian workers, who isolated analogs of **134** derived from primary amines, also reported that they were unstable, but did not investigate the

<sup>369</sup> C. Grundmann and P. Grünanger, "The Nitrile Oxides," p. 69. Springer-Verlag, Berlin and New York, 1971.

<sup>370</sup> L. C. Behr, *Chem. Heterocycl. Compd.* **17**, 310 (1962).

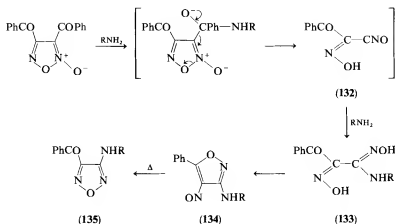
<sup>371</sup> C. Grundmann, R. K. Bansal, and P. S. Osmanski, *Justus Liebigs Ann. Chem.*, 898 (1973).

<sup>372</sup> C. Grundmann, G. W. Nickel, and R. K. Bansal, *Justus Liebigs Ann. Chem.*, 1029 (1975).

<sup>373</sup> C. Ulpiani, *Gazz. Chim. Ital.* **46**, 1 (1916).

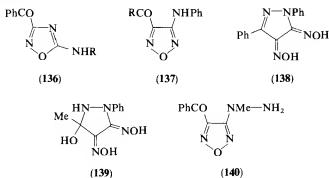
<sup>374</sup> J. Boeseken, *Recl. Trav. Chim. Pays-Bas* **29**, 275 (1910).

<sup>375</sup> A. F. Holleman, *Recl. Trav. Chim. Pays-Bas* **11**, 258 (1892).



SCHEME 6

rearrangement (or decomposition) products.<sup>363</sup> On the other hand, the furazan **135** (R = H) was recognized as the ammonolysis product of dibenzoylfuroxan in 1928<sup>365</sup>; the isoxazole (**134**; R = H) was reported only recently.<sup>364</sup> Alternative 1,2,4-oxadiazole structures (**136**, R = Ph<sup>366,374</sup>; **136**, R = H<sup>376</sup>) were at one time proposed for these furazans, but Bertelson *et al.*<sup>367</sup> favored **135** (R = Ph), and the <sup>13</sup>C NMR of the ammonolysis product seems compatible with **135** rather than **136** (R = H).<sup>363</sup> The reaction of aniline with other diacylfuroxans has been studied, and crude products tentatively identified as the furazans **137** (R = Me and CMe<sub>2</sub>CO<sub>2</sub>Me) were obtained.<sup>367</sup>

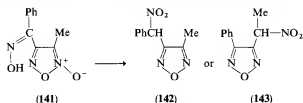


Phenylhydrazine and dibenzoylfuroxan form a red compound which was at one time assigned the nitrosoisoxazole structure **134** (R = NHPh), analogous to the aniline derivative.<sup>170</sup> This reaction was also reinvestigated by Bertelson *et al.*,<sup>367</sup> who suggested a dioximinopyrazoline formula (**138**)

<sup>376</sup> J. Boeseken and D. P. Ross van Lennep, *Recl. Trav. Chim. Pays-Bas* **31**, 196 (1912).

for the product. Diacetylfuroxan initially forms a hydrated derivative (**139**) of the 3-methyl analog of **138**.<sup>367</sup> By contrast, Eremeev *et al.*<sup>363</sup> report the reaction of dibenzoylfuroxan and methylhydrazine to give the hydrazinofurazan **140**. It should be noted that there are a number of unexplained anomalies in the spectra of some of these products: for instance, the UV spectrum of **134** ( $R = Ph$ )<sup>367</sup> compares poorly with those of the aliphatic amine derivatives (**134**;  $R = CHMe_2$ ,  $CMe_3$ ),<sup>363</sup> while the  $^{13}C$ -NMR chemical shifts of **140** are out of line with those of other furazans [e.g., **135** ( $R = H$ )].<sup>363</sup> But, in any event, the hydrazinonitrosoisoxazole structures of type **134** ( $R = NHPh$ ) which have been accepted in number of publications,<sup>87,179,181,183</sup> should be revised.

The oxime of benzoylmethylfuroxan has been reported to rearrange in dilute alkali to the nitrobenzyl furazan **142**.<sup>377</sup> The oxime configuration is apparently *Z*, with the position of the *N*-oxide oxygen atom as shown (**141**).<sup>260</sup> An alternative structure (**143**) for the rearrangement product seems likely: this could arise by a rearrangement analogous to those described for benzofuroxans in Section V.C.4 (see also Ref. 342).



An apparently similar rearrangement is involved in the isomerization of  $\alpha$ -isocyanilic acid (**144**) to  $\beta$ -isocyanilic acid (**145**).<sup>372</sup> However, the configuration of the oxime groups in **144** is assigned as *E*, on evidence that appears to be strong. A further product of the action of hot water on **144**, or, preferably, from thionyl chloride on **145**, is the furazanylfuroxan **146**. In alkali, both rings of **146** are cleaved to form **147**, and this with acid cyclizes again, to give anhydroisocyanilic acid (**148**).<sup>372</sup> Another interesting product, formed by the action of strong alkali on  $\alpha$ - or  $\beta$ -isocyanilic acid, is erythro-cyanilic acid. This was originally assigned a hydroxynitrosopyrazole *N*-oxide formula,<sup>378</sup> but its oximino tautomer (**149**) seems more probable, and the isomeric formula **150** is not ruled out by the evidence.<sup>379</sup> The more recent work of Grundmann *et al.*<sup>372,379</sup> requires a radical revision of the 1971 scheme,<sup>369</sup> and therefore these interconversions and others are summarized here in Scheme 7.

<sup>377</sup> G. Ponzio, *Gazz. Chim. Ital.* **66**, 819 (1936).

<sup>378</sup> H. Wieland, W. Frank, and Z. Kisato, *Justus Liebigs Ann. Chem.* **475**, 42 (1929); H. Wieland, Z. Kisato, and F. Fromm, *ibid.*, 54.

<sup>379</sup> C. Grundmann and J. V. Nelsen, Carnegie-Mellon University, Pittsburgh, Pennsylvania (unpublished work) (1976).





Aqueous alcohol (followed by cupric acetate and then sulfuric acid) was reported by Ponzio to produce 3-benzoylamino-4-phenylfuroxan from 4-phenylfuroxan.<sup>380</sup> Clearly, an extensive degradation has taken place of one of the two molecules of the furoxan involved in the product.

### 3. Benzofuroxans into Quinoxaline Oxides and Benzimidazole Oxides

The earlier review in this series on benzofuroxans appeared just after the first reports on the preparation of quinoxaline dioxides by their reaction with enamines and enolate anions. The succeeding years have seen an immense development in this aspect of their chemistry, stimulated by the discovery that the quinoxaline dioxides have powerful bacteriostatic properties (see Section IX). There are well over a hundred patent registrations concerned with these reactions, for the most part dealing with minor variations in reactants and conditions, and contributing few advances in fundamental knowledge. This review makes no attempt to list and describe patents, except for those for which an equivalent paper in the literature is not available. The reaction has become known, fairly widely, as the Beirut reaction, and it has been reviewed elsewhere, notably by Haddadin and Issidorides<sup>8</sup> and by Ley and Seng.<sup>7</sup> The former also discuss some of the chemistry of the products and the still uncertain mechanism of the reaction; the latter, who deal exclusively with their own work, give useful experimental details for a number of preparations, some of which are unpublished elsewhere. Here we shall simply summarize the main features of the reactions and review the developments in the area since 1976.

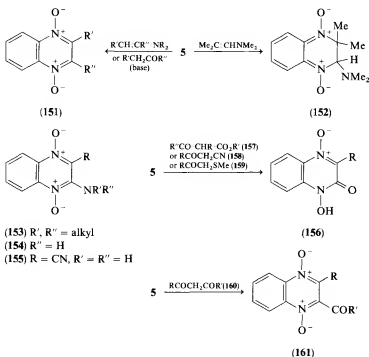
Benzofuroxan (5) reacts under mild conditions with an enamine or with an aldehyde or ketone in the presence of ammonia or an amine to form mono- or disubstituted quinoxaline dioxides (151). Dark red dihydroquinoxaline dioxides (e.g., 152) may be formed when an enamine is used which does not possess an  $\alpha$ -hydrogen atom for elimination.<sup>381</sup> 2-Amino-substituted quinoxaline dioxides have been produced using (a) an ynamine [providing tertiary amines (153)],<sup>382</sup> (b) chloroacetaldehyde and a primary amine [producing secondary amines (154)],<sup>9</sup> and (c) some nitriles, e.g., malononitrile (to give the primary amine 155).<sup>382</sup> The last reaction, however, is by no means a general one, since benzimidazoles are also produced from these substrates (see below). 1-Hydroxyquinoxalin-2-one 4-oxides (156) can also be formed in several ways: using (a) an  $\alpha$ -substituted  $\beta$ -ketoester (157)

<sup>380</sup> G. Ponzio, *Gazz. Chim. Ital.* **66**, 119 (1936).

<sup>381</sup> J. W. McFarland, *J. Org. Chem.* **36**, 1842 (1971).

<sup>382</sup> K. Ley, F. Seng, U. Eholzer, R. Nast, and R. Schubart, *Angew. Chem., Int. Ed. Engl.* **8**, 596 (1969).

(with deacylation)<sup>383</sup>; (b) a  $\beta$ -ketonitrile (**158**) (the cyano group is displaced by  $\text{OH}^-$ )<sup>384</sup>; (c) an  $\alpha$ -(methylthio)ketone (**159**) (the methylthio group is displaced).<sup>338,385</sup> The products (**156**) are also available from *o*-benzoquinone dioximes and  $\alpha$ -ketoaldehydes.<sup>386</sup>



$\beta$ -Diketones (**160**) react with benzofuroxan in the presence of triethylamine to form 2-acylquinoxaline dioxides (**161**). The products from unsymmetrical diketones (**160**;  $\text{R} \neq \text{R}'$ ) have been investigated: steric and electronic effects competitively determine which group forms the acyl and which the quinoxaline substituent, in the product.<sup>383</sup> Sometimes deacylation occurs, particularly when a secondary amine is used as the base or when, as with  $\alpha$ -substituted  $\beta$ -diketones (cf. the  $\beta$ -ketoesters **157**), it is necessary for aromatization.<sup>383,387</sup>

Instead of quinoxaline dioxides, the products are sometimes the mono-N-oxides. Thus, benzofuroxan, morpholine, and cinnamaldehyde (**162**) give

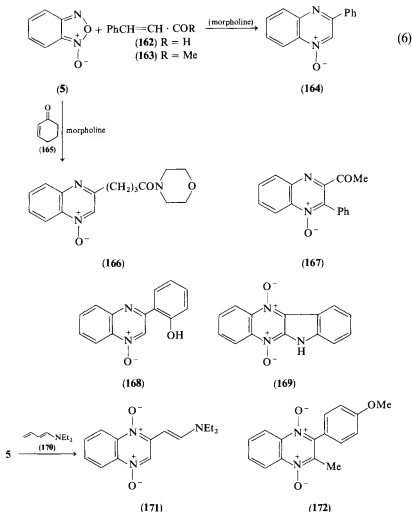
<sup>383</sup> M. J. Haddadin, M. U. Taha, A. A. Jarrar, and C. H. Issidorides, *Tetrahedron* **32**, 719 (1976).

<sup>384</sup> J. C. Mason and G. Tennant, *Chem. Commun.*, 586 (1971).

<sup>385</sup> D. P. Claypool, A. R. Sidani, and K. J. Flanagan, *J. Org. Chem.* **37**, 2372 (1972).

<sup>386</sup> E. Abushanab, *J. Org. Chem.* **35**, 4279 (1970).

<sup>387</sup> R. F. Myers, U. S. Patent 3,947,438 (1976) [*CA* **85**, 21464 (1976)].

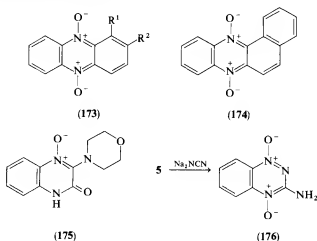


the mono-*N*-oxide **164** (Eq. 6). Here the formyl group is removed by the base, and a similar reaction occurs with benzylideneacetone (**163**), and with cyclohexen-3-one (**165**), which produces the amide **166**.<sup>388</sup> However, the oxidation levels of the products are sometimes not those expected from simple mechanistic considerations. Butylamine, benzofuroxan, and **163** yield the acetyl compound **167**, but with ammonia in place of the amine the corresponding dioxide is produced.<sup>388</sup> Similarly, benzo[*b*]furan-3(2*H*)-

<sup>388</sup> G. S. Lewis and A. F. Kluge, *Tetrahedron Lett.*, 2491 (1977); A. F. Kluge, M. L. Maddox, and G. S. Lewis, *J. Org. Chem.*, **45**, 1909 (1980); *ibid.* **46**, 2603 (1981).

one forms the quinoxaline monoxide **168**, two levels of oxidation lower than expected,<sup>389</sup> while indole gives the fused dioxide **169**,<sup>390</sup> one level higher. An interesting condensation, with oxidation, occurs when the diennamine **170** reacts with benzofuroxan, giving **171**,<sup>391</sup> and anethole (*p*-prop-1-enylanisole), another rather atypical substrate, forms **172**.<sup>337</sup> In these cases it has usually been assumed that benzofuroxan provides the extra oxidation, or the substrate the extra reduction, which is needed.

When phenolate anions are used as substrates, phenazine dioxides are produced. The same product—2-hydroxyphenazine dioxide (**173**;  $R^1 = H$ ,  $R^2 = OH$ )—is formed, whether phenol, resorcinol, hydroquinone, or benzoquinone is used,<sup>9,390,392</sup> illustrating the variability of the relationship between the oxidation levels of the substrates and products. Benzofuroxan, a trialkylphosphine, and a quinone produce blue-violet phosphonium betaine derivatives (e.g., **173**;  $R^1 = PR_3^+$ ,  $R^2 = O^-$ ).<sup>393</sup> The ether **173** ( $R^1 = H$ ,  $R^2 = O\text{-alkyl}$ ) is produced from a hydroquinone mono-ether.<sup>390</sup> 1-Hydroxyphenazine dioxide (**173**;  $R^1 = OH$ ,  $R^2 = H$ ) can be prepared from benzofuroxan, cyclohexane-1,2-dione, and a base, followed by oxidation of the mixture of mono- and di-*N*-oxide formed.<sup>394</sup>  $\beta$ -Naphthol provides benzo[*a*]phenazine dioxide (**174**).<sup>9,390</sup>



<sup>389</sup> J. J. Zamet, M. J. Haddadin, and C. H. Issidorides, *J. C. S. Perkin I*, 1687 (1974).

<sup>390</sup> M. J. Abu El-Haj, B. W. Dominy, J. D. Johnston, M. J. Haddadin, and C. H. Issidorides, *J. Org. Chem.* **37**, 589 (1972).

<sup>391</sup> P. Devi, J. S. Sandhu, and G. Thyagarajan, *J. C. S. Chem. Commun.*, 710 (1979).

<sup>392</sup> M. L. Edwards, R. E. Bambury, and H. K. Kim, *J. Heterocycl. Chem.* **13**, 653 (1976).

<sup>393</sup> K. Ley, F. Seng, and H. Heitzer, *Synthesis*, 258 (1970).

<sup>394</sup> C. H. Issidorides, M. A. Atfah, J. J. Sabounji, A. R. Sidani, and M. J. Haddadin, *Tetrahedron* **34**, 217 (1978).

The formation of unsubstituted quinoxaline 1,4-dioxide in the Beirut reaction has been observed using a number of substrates: benzoylacetaldehyde and its enamines,<sup>395</sup> vinyl acetate ( $\text{Et}_2\text{NH}$ ),<sup>396</sup> acetylene ( $\text{NEt}_3$ )<sup>397,398</sup> propargyl alcohol, propiolic acid, and phenylacetylene (various amines).<sup>398</sup> Some of these are unexceptional, but the apparent dephenylation in the case of the phenylacetylene is surprising. However, recently the reaction of benzofuroxan with diethylamine was reinvestigated<sup>399</sup> (see Section V.E), and quinoxaline dioxide was found to be one of the major products from a complex sequence of oxidation and reduction reactions. It seems probable with phenylacetylene, and possible in other cases too, that the amines play more than a catalytic role in quinoxaline dioxide production. The amino-quinoxalinone **175** was reported, using vinyl acetate and morpholine.<sup>396</sup>

Disodium cyanamide and benzofuroxan form the aminobenzotriazine dioxide **176**, analogously to the malononitrile reaction.<sup>400</sup> If cyanoacetamides are used, however, the reaction takes a different course: instead of becoming included in the ring on cyclization, the cyano group becomes displaced entirely, and 1-hydroxybenzimidazole 3-oxides (**177**) are produced.<sup>401</sup> Reports of the formation of *N*-hydroxybenzimidazoles appeared practically simultaneously from a number of research groups.<sup>338,385,401-405</sup> Primary nitroalkanes (**178**) give the 2-substituted compounds **180**,<sup>404-406</sup> and  $\beta$ -ketosulfones, e.g., **179**, react similarly<sup>385</sup>; deacylation occurs in the latter examples, in which the yields are generally rather poor except for the case where  $\text{R} = \text{H}$ . Secondary nitroalkanes also react, giving the strongly colored 2,2-disubstituted 2*H*-benzimidazole 1,3-dioxides (**181**).<sup>404-406</sup> In these examples the nucleophilic carbon atom of the substrate carries a group  $\text{X}$  ( $\text{CN}$ ,  $\text{SO}_2\text{R}$ ,  $\text{NO}_2$ ) which is able to leave as  $\text{X}^-$ . Benzimidazoles can be formed also when these substituents are lacking; barbituric acid (with  $\text{NaOH}/\text{MeOH}$ ) leads to 1-hydroxybenzimidazole-3-carboxylic acid (**182**),<sup>407</sup> while ethyl acetoacetate forms the ester (**183**), along with the

<sup>395</sup> R. A. Bowie and G. Jones, British Patent 1,301,944 (1973) [*CA* **78**, 97705 (1973)].

<sup>396</sup> A. Monge, A. Llamas, and M. A. Pascual, *An. Quim.* **73**, 1208 (1977) [*CA* **89**, 146871 (1978)].

<sup>397</sup> Z. Lukasiewicz and J. Wrotek, Polish Patent 86,391 (1976) [*CA* **87**, 184550 (1977)].

<sup>398</sup> A. Monge, A. Llamas, and M. A. Pascual, *An. Quim.* **73**, 912 (1977) [*CA* **87**, 184460 (1977)].

<sup>399</sup> M. Z. Nazer, C. H. Issidorides, and M. J. Haddadin, *Tetrahedron* **35**, 681 (1979).

<sup>400</sup> F. Seng and K. Ley, *Angew. Chem., Int. Ed. Engl.* **11**, 1009 (1972).

<sup>401</sup> F. Seng and K. Ley, *Synthesis*, 606 (1972).

<sup>402</sup> C. H. Issidorides and M. J. Haddadin, British Patent 1,215,815 (1970) [*CA* **74**, 141873 (1971)].

<sup>403</sup> W. Duerckheimer, *Justus Liebigs Ann. Chem.* **756**, 145 (1972).

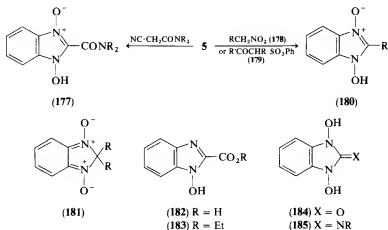
<sup>404</sup> M. J. Abu El-Haj, *J. Org. Chem.* **37**, 2519 (1972).

<sup>405</sup> D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *Chem. Commun.*, 1040 (1972).

<sup>406</sup> D. W. S. Latham, O. Meth-Cohn, H. Suschitzky, and J. A. L. Herbert, *J. C. S. Perkin I*, 470 (1977).

<sup>407</sup> F. Seng and K. Ley, *Synthesis*, 703 (1975).

quinoxaline dioxide (**161**;  $R = \text{Me}$ ,  $R' = \text{OEt}$ ), in proportions which depend on the conditions used.<sup>403</sup> These benzimidazoles are at a lower level of oxidation than in **177**. Further examples of this ring system arise when benzofuroxan is treated with formaldehyde and alkali (giving **184**),<sup>408</sup> or with formaldehyde and a primary amine or with a hexahydro-1,3,5-triazine (giving **185**).<sup>409</sup> Diphenyldiazomethane and benzofuroxan give the dioxide **181** ( $R = \text{Ph}$ ), the corresponding monoxide, and/or 1,2-diphenylbenzimidazole, depending on the temperature of the reaction.<sup>339</sup>



A fairly wide variety of 5-substituted benzofuroxans have been reported to undergo condensations of the types described above. The 5-nitro compound is unsuccessful, but 5-halo-, -methoxy-, -methyl-, -sulfonamido-, -formyl-, -acetyl-, -trifluoromethyl-, -cyano-, and -carboxy-substituted benzofuroxans form the respective quinoxaline or benzimidazole derivatives. 4-Substituted benzofuroxans, on the other hand, generally do not undergo the reactions<sup>8</sup> (although not many seem to have been tried). Of the heterocyclic-ring-fused furoxans, the thieno compound (**92**) with malononitrile has been reported to give a low yield of the aminonitrile **186**,<sup>258</sup> the fused pyrimidine **66** with anilines forms alloxazine derivatives **187**,<sup>410</sup> and some other pyrido- (**101**) and pyrimidofuroxans (**188**;  $R = \text{NH}_2$ ,  $\text{OMe}$ ) are reported to condense with ketones, in the presence of dimethylamine, to form pyrido- and pyrimidopyrazine dioxides (**189**).<sup>411</sup> In some of these examples the authors explained their results by invoking reaction of the

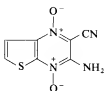
<sup>408</sup> F. Seng and K. Ley, *Angew. Chem., Int. Ed. Engl.* **11**, 1009 (1972).

<sup>409</sup> F. Seng, K. Ley, and K. Wagner, *Synthesis*, 703 (1975).

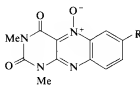
<sup>410</sup> F. Yoneda, Y. Sakuma, and S. Matsumoto, *Heterocycles* **3**, 113 (1975).

<sup>411</sup> D. Binder, *Ger. Offen.* 2,703,369 (1977) [*CA* **87**, 152274 (1977)].

less favorable tautomers of the reactant furoxans; however, in the thienofused case there seems no reason to select **186**, rather than the 2-amino-3-cyano isomer, as the product.



(186)



(187)



(188)



(189) X = N, CH

The mechanism of these reactions was discussed by Haddadin and Issidorides<sup>8</sup> in 1976, and no new evidence or significant argument has come to light since that time. Most authors accept an intermediate of type **190**, formed by attack of the nucleophilic reagent on the benzofuroxan—either in its ground state (**5**) or in the dinitroso form (**191**). If the ground state is involved, as argued by Mason and Tennant,<sup>384</sup> a substituted benzofuroxan usually has two forms available; although these authors favor the major tautomer as the species undergoing attack, others<sup>258,410</sup> suggest the minor. The intermediate **190** could be formed by nucleophilic attack either at N(1) (a) or at N(3) (b) (Scheme 8). That N(3) can be so attacked is shown by the reaction with dialkylamines, which produces *o*-nitrophenylhydrazine derivatives (see Section V,E); however, in this case the subsequent bond reorganization follows a different course. Reaction at N(1), while unambiguously leading to **190**, does not seem appealing and has not attracted noticeable support.

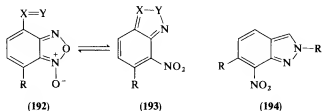
An alternative pathway to **190** lies through the dinitrosobenzene (**191**), as Abushanab and Alteri suggested.<sup>338</sup> The case for this route would be strengthened if **191** could be shown to be a species having an appreciable lifetime, but evidence on this so far has been negative (Section V,B,1). In its favor is the fact that only the rapidly equilibrating fused furoxans undergo the Beirut reaction; no reaction occurs, for instance, with naphthofuroxan (**16**). But 4-substituted benzofuroxans, which also equilibrate rapidly, appear





#### 4. Benzofuroxans into Other Benzo-Fused Heterocyclic Systems

In this section we discuss further examples of the rearrangement of 4-substituted benzofuroxans (**192**) into nitroheterocycles (**193**). The previous review in this series<sup>6</sup> summarized results which were published up to 1968.



It has since been shown that the equilibrium between 4-formylbenzofuroxan and 7-nitroanthranil (**192**  $\rightleftharpoons$  **193**; X = CH, Y = O, R = H) contains a substantial proportion (*ca*  $\sim$  40% at 100°C) of the furoxan **192**.<sup>413</sup> Chloro<sup>414</sup> and methoxy<sup>105,413</sup> substituents R lead to a large preference for the formylbenzofuroxan form. These aldehydes (**192**; X = CH, Y = O, R = H, Cl or OMe) condense readily with primary amines, followed by rearrangement of the type indicated, to provide indazoles **194**.<sup>413</sup> The intermediate imines (**192**; X = CH, Y = NR') could not be isolated when R was alkyl or aryl, but hydroxylamine and hydrazine derivatives condensed to give isolable derivatives of the formyl group, which thermally rearranged to the 2-oxy- and 2-amino-substituted indazoles (**194**).<sup>105</sup> The equilibration of 4-ethoxycarbonylamino-5,7-dinitrobenzofuroxan with the 4,6-dinitro-5-urethane has been studied.<sup>415</sup> A report that 5-fluoro-4-nitrobenzofuroxan (**193**; X = NO, Y = O, R = F) does not rearrange thermally<sup>416</sup> is erroneous: the authors had inadvertently obtained the 5-hydroxy compound.<sup>417</sup> The equilibrium (**192**  $\rightleftharpoons$  **193**) of the potassium salt of this hydroxy compound (X = NO, Y = O, R = O<sup>-</sup>K<sup>+</sup>) has been studied by another group. In water, form **193** is favored, to the extent of approximately 10:1, but on heating in the solid phase the potassium salt **193** forms **192**.<sup>418</sup>

<sup>413</sup> S. N. Balasubrahmanyam, A. S. Radhakrishna, A. J. Boulton, and K. W. Thoe, *J. Org. Chem.* **42**, 897 (1977).

<sup>414</sup> A. J. Boulton and R. C. Brown, *J. Org. Chem.* **35**, 1662 (1970).

<sup>415</sup> T. P. Hobin, *Tetrahedron* **24**, 6125 (1968).

<sup>416</sup> P. B. Ghosh, B. Ternai, and M. W. Whitehouse, *J. Med. Chem.* **15**, 255 (1972).

<sup>417</sup> P. B. Ghosh, personal communication.

<sup>418</sup> E. Bunce, N. Chuaqui-Offermanns, and A. R. Norris, *Can. J. Chem.* **57**, 2512 (1979).

## D. REDUCTION

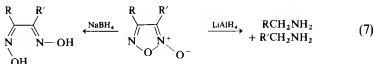
Furoxans can be reduced in a variety of ways, depending upon the conditions used. The earlier review of Boyer<sup>4</sup> covers the previous work well; here we illustrate the possibilities mainly by examples from the more recent literature.

1. *Catalytic Hydrogenation*

Hydrogenation of furoxans over a metal catalyst usually leads to dioximes, but sometimes more far-reaching reduction occurs, with C—C and/or N—O cleavage, yielding diamines. Camphorfuroxan (13), formerly thought to be a single isomer (but see Ref. 97), is said to be reduced to a single dioxime.<sup>419</sup> Tetrahydrobenzofuroxan forms cyclohexanedione dioxime (Pd/C, 20°C), or hexamethylenediamine (Raney Ni, 100°C), depending on the conditions.<sup>279,420</sup> Dioximes have also been formed from diaroylfuroxans (Pt<sup>419</sup> or Pd<sup>421</sup>), 3-amino-4-phenylfuroxan (Pd/C),<sup>86</sup> 3-arylfuroxan-4-carboxamides (Pd/BaSO<sub>4</sub>) and their isomers (Pd/C),<sup>259</sup> and from 3-aryl-4-methylfuroxans (Pt).<sup>259</sup> The reported<sup>286</sup> reduction (Pt) of 3-methyl-4-nitrofuroxan to the amine, leaving the furoxan ring intact, is probably incorrect (see Section VII.B).

2. *Reduction with Complex Hydrides*

Dialkyl- and diarylfuroxans and benzofuroxans are reduced by sodium borohydride to the dioximes,<sup>422</sup> while acylfuroxans can be converted into the corresponding furoxan alcohols.<sup>80,422</sup> The more vigorous reducing agent lithium aluminum hydride cleaves the ring C—C bond, giving amines (Eq. 7)<sup>182,283,423,424</sup>; this reaction is considered again in Section V.E.



<sup>419</sup> D. Bigiavi, *Gazz. Chim. Ital.* **51**, 324 (1921).

<sup>420</sup> D. Klamann and W. Siemens, *Chem.-Ing.-Tech.* **39**, 511 (1967).

<sup>421</sup> H. Tondys and J. Lange, *Rocz. Chem.* **51**, 1531 (1977) [*CA* **88**, 50735 (1978)].

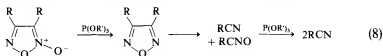
<sup>422</sup> J. H. Boyer and S. E. Ellzey, *J. Am. Chem. Soc.* **82**, 2525 (1960).

<sup>423</sup> A. Dornow, K. J. Fust, and H. D. Jordan, *Chem. Ber.* **90**, 2124 (1957).

<sup>424</sup> A. R. Daniewski, M. Witanowski, and T. Urbanski, *J. Org. Chem.* **32**, 4050 (1967).

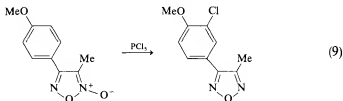
### 3. Reduction with Phosphorus Compounds

Tervalent phosphorus compounds (phosphorous derivatives) are well-established reagents for the deoxygenation of amine oxides and nitrones, and they provide a clean and convenient method for the preparation of furazans from furoxans. Mukaiyama *et al.*<sup>425</sup> and Grundmann<sup>426</sup> used trialkylphosphites, and they have been widely employed since that time, both with and without solvents.<sup>80,85,93,95,97,352</sup> The simple dialkyl- and diarylfuroxans usually require more vigorous conditions (e.g., refluxing triethyl phosphite) than do strained derivatives or the benzofuroxans.<sup>85,97</sup>



Phosphite deoxygenation of acenaphthofuroxan to the furazan occurs at room temperature. The product ring-opens on mild heating, and further reduction produces the dinitrile (naphthalonitrile).<sup>427</sup> Presumably the same order of events occurs with unstrained furoxans, which, under more vigorous conditions (e.g., in refluxing triphenyl phosphite), yield the nitriles directly<sup>427,428</sup> (Eq. 8).

Other P(III) derivatives deoxygenate furoxans, including trialkyl and triaryl phosphines<sup>426</sup> (contrary to another report<sup>429</sup>). Early workers occasionally used phosphorus pentachloride, Ponzio believing that the reaction served to distinguish between furoxans, which could be deoxygenated, and dioxadiazines, which could not.<sup>19,23-26</sup> The deoxygenation is no doubt a reaction of phosphorus trichloride, produced by dissociation of the pentachloride, and, when an aryl group is present which is activated toward electrophilic attack, chlorination also occurs<sup>19,25</sup> (Eq. 9). Phosphorus sulfides have also been used for furoxan deoxygenation,<sup>274,276</sup> as



<sup>425</sup> T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.* **27**, 3651 (1962).

<sup>426</sup> C. Grundmann, *Chem. Ber.* **97**, 575 (1964).

<sup>427</sup> A. J. Boulton and S. S. Mathur, *J. Org. Chem.* **38**, 1054 (1973).

<sup>428</sup> S. M. Katzman and J. Moffat, *J. Org. Chem.* **37**, 1842 (1972).

<sup>429</sup> J. H. Boyer and S. E. Ellzey, *J. Org. Chem.* **26**, 4684 (1961).

have red phosphorus and hydrogen iodide.<sup>430</sup> More extensive reduction occurs when dipyrimidylfuroxans are treated with phosphonium iodide and hydriodic acid, which converts the furoxan ring into a 1,2-diaminoethane.<sup>203</sup>

#### 4. Reduction with Dissolving Metals and Metal Ions

The reduction of furoxans by dissolving metals has frequently been accomplished. Zinc and acetic acid<sup>19,87,259,260,272-274,276,277,317,353,419</sup> and tin and hydrochloric acid<sup>273,274,276-278,353</sup> are the most commonly used reagents. The reduction products are usually dioximes (in some cases in the expected amphi configuration, in others in a different form), or furazans, probably arising as secondary products by dehydration of the dioximes. Zinc with acetic acid is reported to convert dibenzoylfuroxan into 1,2-dibenzoylthane.<sup>431</sup> Stannous chloride in acid has often been used for the reduction to furazans.<sup>355, 365, 421, 432</sup>

#### 5. Electrochemical and Other Reducing Methods

The electrochemical reduction of a number of furoxan derivatives has been studied polarographically. The products depend on the pH of the medium. Benzofuroxan appears to be reduced first to the dioxime anion and then further to diaminophenazine and *o*-phenylenediamine.<sup>138,433,434</sup> Naphthofuroxan behaves similarly, in that the number of waves which are observed depends on the acidity and that the dioxime is the first product.<sup>433</sup> Other electroreduction experiments have been carried out, particularly with bibenzofuroxan sulfone, with a view to the development of a reversible depolarizer for nonaqueous battery systems.<sup>435-437</sup> The results of ESR measurements on the electrochemical reduction products of several furoxans are mentioned in Section III,E.

<sup>430</sup> K. von Auwers and V. Meyer, *Ber. Dtsch. Chem. Ges.* **21**, 784 (1888).

<sup>431</sup> A. F. Holleman, *Recl. Trav. Chim. Pays-Bas* **10**, 211 (1890).

<sup>432</sup> C. Lehmann, E. Renk, and A. Gagneux, Swiss Patents 498137, 498857 (1970) [CA **74**, 100061, 100067 (1971)].

<sup>433</sup> E. S. Levin, Z. I. Fodiman, and Z. V. Todres, *Elektrokhimiya* **2**, 175 (1966) [CA **65**, 5022 (1966)].

<sup>434</sup> C. D. Thompson and R. T. Foley, *J. Electrochem. Soc.* **119**, 177 (1972) [CA **76**, 80184 (1972)].

<sup>435</sup> R. T. Foley and F. D. Bogar, *NASA Contract Rep.* MASA CR-94736 (1968); *Sci. Tech. Aerosp. Rep.* **6**, 2212 (1968) [CA **71**, 76647 (1969)].

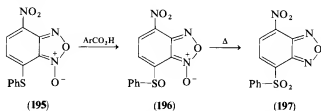
<sup>436</sup> J. T. Shaw, U.S. Patents 3,260,621 (1966), 3,528,098 (1970) [CA **65**, 10130 (1966); **74**, 9113 (1971)].

<sup>437</sup> R. T. Foley, D. H. Bomkamp, and C. D. Thompson, *U.S. N. T. I. S., AD Rep.* AD-740210 (1972); *Gov. Rep. Announce. (U.S.)* **72**, 102 (1972) [CA **77**, 96228 (1972)].

Thiols reduce benzofuroxan to the dioxime: this reaction was suggested as a means of quantitative estimation of thiol groups in enzymes.<sup>438,439</sup> The dioximes may be conveniently prepared by hydrazobenzene reduction of the benzofuroxans.<sup>440</sup>

Sodium azide in ethylene glycol<sup>441</sup> or acetic or isobutyric acid<sup>442</sup> is reported to deoxygenate benzofuroxans to the furazans. Thermal deoxygenations of benzofuroxans has also been observed, in a few special cases.<sup>310</sup>

When 4-nitro-7-phenylthiobenzofuroxan (**195**) was oxidized by *m*-chloroperbenzoic acid, an intramolecular redox reaction resulted in the formation of the benzofurazan sulfone (**197**).<sup>443</sup> It has been shown that the sulfoxide (**196**) (and a number of analogous compounds) can be isolated, and that it is thermally converted into **197**.<sup>444</sup> This result is interesting in view of the reported failure to observe intramolecular oxygen transfer in a number of fused furoxans.<sup>350,445</sup>



Other reagents which can effect reduction of furoxans include iodide ion,<sup>83,446</sup> sulfur dioxide,<sup>247,279</sup> and ammonium sulfide.<sup>196</sup>

### E. REACTION WITH GRIGNARD REAGENTS

There are a number of references in the older literature to the reaction of Grignard reagents with furoxans. The earlier reviews<sup>3-5</sup> are all in some respects incomplete, and occasionally also misleading, so we shall discuss here all the work which has come to our attention.

<sup>438</sup> M. Shipton, T. Stuchbury, K. Brocklehurst, J. A. L. Herbert, and H. Suschitzky, *Biochem. J.* **161**, 627 (1977).

<sup>439</sup> M. Shipton and K. Brocklehurst, *Biochem. J.* **167**, 799 (1977).

<sup>440</sup> M. M. El-Abadelah, Z. H. Khan, and A. A. Anani, *Synthesis*, 146 (1980).

<sup>441</sup> L. DiNunno, S. Florio, and P. E. Todesco, *J. C. S. Perkin I*, 1954 (1973).

<sup>442</sup> L. DiNunno and S. Florio, *Chim. Ind. (Milan)* **57**, 543 (1975) [*CA* **84**, 90088 (1976)].

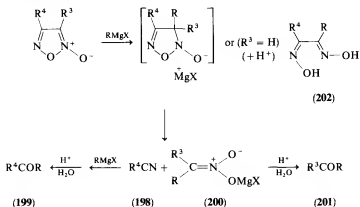
<sup>443</sup> P. B. Ghosh, *J. Chem. Soc. B*, 334 (1968).

<sup>444</sup> J. G. Belton, *Proc. R. Ir. Acad.* **74B**, 185 (1974) [*CA* **81**, 152118 (1974)].

<sup>445</sup> A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *J. Chem. Soc. C*, 1193 (1971).

<sup>446</sup> M. A. Bianco, A. Gasco, V. Mortarini, A. Serafino, and E. Menziani, *Farmaco, Ed. Sci.* **28**, 701 (1973).

Wieland and Semper were the first to study the reaction.<sup>19</sup> They reported that methylmagnesium iodide gave yellow insoluble adducts with anisyl-methylfuroxan and diphenylfuroxan, which on hydrolysis re-formed the original furoxans. Other workers, led by Angeli, contradicted this, saying that the reaction is a vigorous one, but sometimes with an induction period. Angeli investigated the action of phenylmagnesium bromide on 3-methyl-4-(3,4-methylenedioxyphenyl)furoxan,<sup>447</sup> and Bigiavi treated the same furoxan with methylmagnesium iodide, and also 4-anisyl-3-methylfuroxan with phenylmagnesium bromide.<sup>419</sup> Both workers observed the aryl cyanide (198) and the aryl ketone derived from the Grignard reagent (199) among the products, along with ammonia and, from phenylmagnesium bromide, a water-soluble compound which provided acetophenone on hydrolysis and which was tentatively identified as the nitronate salt (200; R = Ph, R<sup>3</sup> = Me). Later, after the isomerism of arylmethylfuroxans was discovered, Ponzio and Longo<sup>448</sup> treated isomeric pairs with ethyl- and methylmagnesium iodide, using more vigorous work-up conditions (steam distillation) than the earlier workers. From a 4-aryl-3-methylfuroxan they isolated the aryl cyanide and acetone or methyl ethyl ketone (201; R<sup>3</sup> = Me), while the same reagents with an "arylmethyldioxadiazine" (i.e., a 3-aryl-4-methylfuroxan) provided the aryl ketone (201; R<sup>3</sup> = Ar) and the methyl ketone (199; R<sup>4</sup> = Me) (Scheme 9).



SCHEME 9

All the above reactions proceed with C—C bond cleavage of the furoxan ring, and Dornow *et al.*<sup>423</sup> pointed out that the C—C fission which they observed in the lithium aluminum hydride reduction of furoxans could take

<sup>447</sup> A. Angeli, *Gazz. Chim. Ital.* **46** (2), 300 (1916).

<sup>448</sup> G. Ponzio and G. Longo, *Gazz. Chim. Ital.* **60**, 893 (1930).

place analogously, by addition of the Grignard carbanion, or the hydride ion, to C-3 of the furoxan ring, followed by a cycloreversion to cyanide and nitronate anion, as indicated in Scheme 9. In the case of the Grignard reactions, some of the cyanide reacts further to give aryl ketone, as Bigiavi suggested,<sup>419</sup> while the hydride reduces both fragments to the amines.

Not all furoxan reactions conform to this pattern. The two isomers of phenylfuroxan (see Section VI) were studied by Ponzio, whose account is rendered somewhat obscure by his uncertainty over their structures. It is now clear that his " $\alpha$ -peroxide" is 4-phenylfuroxan, and that with methylmagnesium iodide it forms  $\alpha$ -methylphenylglyoxime (**202**)<sup>380,449</sup> while the  $\beta$ -isomer is 3-phenylfuroxan, and it behaves more normally, in that with the methyl Grignard reagent acetophenone is formed,<sup>30</sup> possibly according to Scheme 9. 4-Phenylfuroxan decomposes very easily, particularly under basic conditions, to the nitrile oxide **120**, and it is not known whether the glyoxime **202** is formed via **120**, or by direct attack of the Grignard reagent on the furoxan, since Ponzio showed that **120** also forms the  $\alpha$ -glyoxime (**202**) with methylmagnesium iodide.<sup>450</sup>

A further investigation of Grignard reactivity with furoxans was undertaken by Kinney,<sup>269</sup> who treated diphenylfuroxan with phenylmagnesium bromide. In this case, perhaps because of steric effects, the reaction took a different course again, and phenol and biphenyl were the principal products isolated.

## F. MISCELLANEOUS REACTIONS OF THE FUROXAN RING

In Section V,C,3 some reactions of benzofuroxan were described which in all likelihood involve nucleophilic attack at N(3), followed by ring opening and recyclization. With a few reagents nucleophilic attack at N(3) precedes ring opening in a different sense, and recyclization does not follow. Thus, secondary amines react with benzofuroxan to form substituted *o*-nitrophenylhydrazines (**203**),<sup>451-453</sup> Similarly, dimethyl sulfoxide and pyridofuroxan (**101**) give the sulfoximine **204**.<sup>454</sup> The reaction with diethylamine has been reinvestigated more recently,<sup>399</sup> and, besides the hydrazine (**203**; R = Et), a number of other products were found, including quinoxaline dioxide (**151**; R' = R'' = H), which was mentioned earlier, 3-methyl-1,2,4-benzotriazine (**205**) and its 4-oxide, *o*-benzoquinone dioxime, *o*-nitro- and

<sup>449</sup> G. Ponzio, *Gazz. Chim. Ital.* **53**, 507 (1923).

<sup>450</sup> G. Ponzio, *Gazz. Chim. Ital.* **66**, 127 (1936).

<sup>451</sup> D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *Tetrahedron Lett.*, 5365 (1972).

<sup>452</sup> D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 2216 (1976).

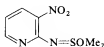
<sup>453</sup> D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *J. C. S. Perkin I*, 478 (1977).

<sup>454</sup> B. Stanovnik and M. Tisler, *Chimia* **25**, 272 (1971).

*o*-nitrosoaniline, and benzofurazan. Other benzofuroxans (5-Cl, 5-CF<sub>3</sub>) gave substituted hydrazines, along with products derived from nucleophilic attack at the benzene ring (see Section VIII), when treated with a variety of secondary amines.<sup>452</sup>



(203)



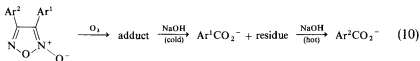
(204)



(205)

The surprising claim<sup>83</sup> that furoxans in general are reversibly ring-opened by hydroxide ion to  $\alpha$ -nitroketoxime anions requires further investigation.

The ozonolysis of diarylfuroxans was studied by Kinney and Harwood. In their earlier paper,<sup>272</sup> they found that benzoic acid was formed from diphenylfuroxan, and they interpreted this as evidence for the presence of a C=C bond in the heterocyclic ring, as in structure 4. Later, the isolation of isomeric anisylphenylfuroxans by Meisenheimer *et al.*<sup>22</sup> came to their attention, and Kinney<sup>269</sup> subjected the two forms to ozonolysis. Both formed a yellow ozone adduct of unknown composition, which with cold dilute sodium hydroxide gave the salt of the acid derived from the 3-substituent, together with a red residue which on further hydrolysis with hot hydroxide formed the acid of the 4-substituent (Eq. 10). This work provided valuable support for Meisenheimer's contention that his compounds were positional isomers, both based on the furoxan ring structure (1).



## VI. Monosubstituted Furoxans

Unsubstituted furoxan (1; R<sup>1</sup> = R<sup>2</sup> = H) is unknown. Fulminic acid (HCNO) oligomerizes readily, but the products are mainly trimers and tetramers; they are summarized in part in Section V,C, and elsewhere.<sup>369,370</sup> Monosubstituted furoxans are labile compounds, but some have been reported (not all of them reliably). The best studied are the phenylfuroxans, on which there is an extensive literature, much of it extremely confused, since Ponzio worked on the compounds for some 20 years, over which period his views on their structures changed several times, and it was only at the end that he accepted that any contained a furoxan ring.

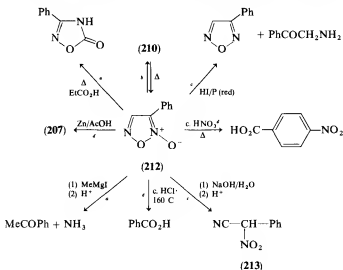
A phenylfuroxan (or a structure which would now be written as such) was first reported by Scholl,<sup>190</sup> and later by Wieland and Semper,<sup>19</sup> by oxidation of  $\alpha$ -phenylglyoxime (206) with dinitrogen tetroxide. Phenylacetylene and





NMR,<sup>108</sup> and by Gagneux and Meier,<sup>86</sup> who found that the  $\alpha$ -glyoxime was conveniently oxidized to the furoxan by ceric ammonium nitrate. The products of the reactions of **210** are summarized in Scheme 10. Most of these are likely to be formed through the intermediacy of the nitrile oxide (**211**), or a derivative (e.g., the oximate anion) of this. 4-Phenylfuroxan is a very unstable compound, and in some solvents it decomposes, at least in part, to **211** without addition of base.<sup>362</sup> Compound **211** was first isolated by Wieland and Semper, but they assigned to it a hydroxyfuran structure (**209**).<sup>19</sup> 4-Phenylfuroxan was found not to be quaternized by methyl iodide or dimethyl sulfate (in common with all other simple furoxans), nor to isomerize in ultraviolet light.<sup>362</sup>

When 4-phenylfuroxan is heated, alone,<sup>456</sup> or, better, in refluxing xylene<sup>380</sup> or in 1,1,1,2-tetrachloroethane,<sup>107</sup> it forms the 3-phenyl compound (**212**) (mp 108°C). The conversion yield is rather low because **210** also decomposes irreversibly to **211**.<sup>107</sup> The new isomer (**212**), which can also be prepared by nitric acid oxidation of the  $\beta$ -glyoxime (**207**),<sup>457</sup> shows a marked contrast in properties with those of **210**. It has not been investigated as fully as the 4-phenyl compound; the products from a number of its reactions are shown in Scheme 11. On heating in 1,1,1,2-tetrachloroethane, it partially reverts



<sup>a</sup> Ref. 30. <sup>b</sup> Ref. 107. <sup>c</sup> Ref. 456. <sup>d</sup> Ref. 457.

SCHEME 11

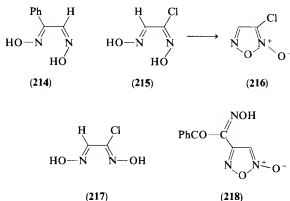
<sup>456</sup> G. Ponzio and L. Avogadro, *Gazz. Chim. Ital.* **57**, 124 (1927).

<sup>457</sup> G. Ponzio, *Gazz. Chim. Ital.* **55**, 698 (1925).

to **210**.<sup>107</sup> Compound **212** seems to be rather more stable than **210** toward ring-cleavage; provided that the medium is kept acidic, it can be steam-distilled.<sup>457</sup> Its decomposition by base to the anion of  $\alpha$ -nitrophenylacetonitrile (**213**), discovered by Ponzio,<sup>456</sup> should be considered good evidence for the structure **212**. Nevertheless, as late as 1936, when he was convinced that he had three isomers (viz., **210**, **211**, and **212**), he would assign to none a furoxan structure, preferring to suggest that one might be accommodated by a 1,2-dinitrosoethylene formula.<sup>30</sup> (See Section X.)

Three isomers have also been observed in the *p*-tolyl series. Although the early literature on the " $\alpha$ -form" is very much confused between "peroxide" and nitrile oxide structures,<sup>456-458</sup> in his final paper<sup>459</sup> Ponzio almost completely clarified the matter, both identifying the nitrile oxide (corresponding to **211**) and assigning a 4-arylfuroxan formula to Avogadro's original product.<sup>458</sup> The  $\beta$ -isomer, which was prepared by nitric acid oxidation of the  $\beta$ -form of the dioxime, appears to be 3-*p*-tolylfuroxan, analogous to **212**.<sup>456</sup>

The  $\beta$ -glyoximes, from which the 3-arylfuroxans are prepared, have been assigned the anti structures (cf. **207**). It seems rather surprising that the same glyoximes are re-formed on reduction (Zn/AcOH) of the 3-arylfuroxans.<sup>456,457</sup> However, the expected isomer is the unknown 1-*E*-2-*Z*-amphi form (**214**); possibly this is formed, but rearranges quickly to **207**. Ungnade and Kissinger<sup>83</sup> assigned their product from the oxidation of *amphi*-chloroglyoxime (**215**) as 3-chlorofuroxan (**216**) because it very readily oxidized iodide ion, at a rate comparable with that of dichlorofuroxan, while other chlorofuroxans, presumed to be 4-chloro compounds, were much less reactive (see Section VII,C). The *anti*-chloroglyoxime isomer (**217**), with



<sup>458</sup> L. Avogadro, *Gazz. Chim. Ital.* **53**, 824 (1923).

<sup>459</sup> G. Ponzio, *Gazz. Chim. Ital.* **71**, 693 (1941).

configuration corresponding to that assigned to the  $\beta$ -aryl glyoximes,<sup>460</sup> by contrast gave only a small quantity of chlorofuroxan.

From the fulminic acid oligomer studies of Wieland, Grundmann *et al.*, two 3-monosubstituted furoxans have been reported. These are the precursor (127) of prefulminuric acid,<sup>371</sup> and, in the cyanilic acid field, the furoxan 146.<sup>372</sup> The methylfuroxan prepared by oxidation ( $N_2O_4$ ) of methylglyoxime<sup>190</sup> and the corresponding propylfuroxan<sup>461</sup> were not isolated pure and are of undetermined structure.

Some further monosubstituted furoxans which have been reported are either of very doubtful authenticity or have been discredited. The phenacyl derivatives of Harries and Tietz,<sup>462</sup> formed by the nitrosation of  $\beta$ -aryl- $\alpha,\beta$ -unsaturated oximes, have been shown to be pyrazolone di-*N*-oxides.<sup>463</sup> The degradation of "Holleman's peroxide" (29) by hydroxylamine and alkali was reported to form structure 218, or its 3-substituted isomer, by Boyer and Chang.<sup>29</sup> It does, however, seem unlikely that a monosubstituted furoxan could withstand such reaction conditions. Decarboxylation of furoxandicarboxylic acid has been suggested to provide the 4-monocarboxylic acid,<sup>464</sup> but Ponzio and De Paolini<sup>465</sup> have assigned a nitrile oxide structure to the product.

## VII. Disubstituted Furoxans: Reactions of Substituents

In this section we consider briefly the principal substituent groups on the furoxan ring and the reactions they undergo.

### A. ALKYL AND ARYL FUROXANS

Although a large number of dialkyl-, diaryl-, and alkylarylfuroxans are known, the chemical behavior of the substituents has not received much attention. Aryl groups can be brominated, chlorinated, and nitrated, particularly when one or more electron-releasing groups are present.<sup>23, 24, 26, 274-278, 353</sup> Potassium permanganate oxidizes some 4-aryl-3-methylfuroxans to 3-methylfuroxan-4-carboxylic acid.<sup>93, 466</sup>

<sup>460</sup> H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron* **19**, Suppl. 1, 235 (1963).

<sup>461</sup> J. F. Brown, *J. Am. Chem. Soc.* **77**, 6341 (1955).

<sup>462</sup> C. Harries and H. Tietz, *Justus Liebigs Ann. Chem.* **330**, 237 (1904).

<sup>463</sup> J. P. Freeman and D. L. Surbey, *Tetrahedron Lett.*, 4917 (1967); J. P. Freeman, J. J. Gannon, and D. L. Surbey, *J. Org. Chem.* **34**, 187 (1969).

<sup>464</sup> H. Wieland, L. Semper, and E. Gmelin, *Justus Liebigs Ann. Chem.* **367**, 52 (1909).

<sup>465</sup> G. Ponzio and I. De Paolini, *Gazz. Chim. Ital.* **56**, 247 (1926).

<sup>466</sup> A. Angeli, *Ber., Dtsch. Chem. Ges.* **26**, 593 (1893).

The isoxazolinic transposition, which incorporates the methyl carbon atom of 4-aryl- (and benzyl-) -3-methylfuroxans into the ring (Eq. 5) is described in Section V,C,1; so far only methyl groups have been found to undergo this reaction. It provides a clear distinction between 4-aryl-3-methylfuroxans and the 3-aryl-4-methyl isomers, which Ponzio thought were dioxadiazines (2). After a thorough investigation, he concluded that those compounds which underwent the isoxazolinic transposition, which gave furazans with phosphorus pentachloride, and which showed the higher melting point, were furoxans, while the dioxadiazines showed neither of the reactions and melted at the lower temperatures.<sup>23,25</sup> It is clear that he never attached much weight to the melting-point observation; however, in an earlier review it was applied as the sole criterion of distinction between the two series.<sup>467</sup> In fact, the higher melting anisyl-methyl isomer on bromination forms the lower melting of the bromoanisyl-methyl isomers, and both were correctly assigned by Ponzio as 4-aryl-3-methylfuroxans because they both rearrange in alkali.<sup>23</sup>

## B. AMINOFUROXANS

A few aryl<sup>86,288,468,469</sup> and aroyl<sup>365</sup> aminofuroxans, and bisdialkylaminofuroxans,<sup>84</sup> have been reported. Except for a few examples, the structures of the compounds are well established. Aminophenylfuroxans in the early literature probably refer, in one instance,<sup>288</sup> to the 4-amino-3-phenyl isomer, and in another,<sup>468</sup> to the 3-amino-4-phenyl compound. A report<sup>286</sup> that 3-methyl-4-nitrofuroxan is reduced catalytically (Pt/H<sub>2</sub>; AcOH) to the amine is probably incorrect: the 4-amino-3-methyl compound obtained by hydrolysis of its *O*-benzylurethane has different properties.<sup>470</sup> The 3-aminofuroxans are rather easily converted by heat into the 4-amino isomers (see Section V,B).

Although 4-amino-3-arylfuroxans can be acylated normally, the 3-amino isomers do not readily form amides.<sup>86</sup> Oxidation (85% H<sub>2</sub>O<sub>2</sub>/CF<sub>3</sub>CO<sub>2</sub>H) of 4-amino-3-phenylfuroxan affords the 4-nitro derivative, but the isomeric 3-amino compound provides a mixture of the 3-nitrofuroxan and 3-nitro-4-phenylfurazan.<sup>471</sup>

<sup>467</sup> J. V. R. Kaufman and J. P. Picard, *Chem. Rev.* **59**, 437 (1959).

<sup>468</sup> A. Vianello, *Gazz. Chim. Ital.* **58**, 326 (1928).

<sup>469</sup> C. Lehmann, A. Gagneux, and E. Renk, Swiss Patents 496,721, 496,722, 497,444 (1970) [*CA* **75**, 5908, 20406, 36057 (1971)].

<sup>470</sup> D. Furlani, Dipl. Chem. Pharm. Thesis, University of Turin (1978).

<sup>471</sup> G. Chiarabaglio, Dipl. Pharm. Thesis, University of Turin (1978).

## C. HALOGENOFUROXANS

Difluorofuroxan is unknown. The other three symmetrical dihalofuroxans have been made by the action of the appropriate halogen on a fulminate salt (see Section IV.A.6), or by dehydrohalogenation and dimerization of dihaloformaldoximes.<sup>227,472</sup> Monochloro compounds are prepared by oxidation of chloroglyoximes<sup>83,473</sup>; their structures were assigned on the basis of reactivity comparisons<sup>83</sup> (apart from the early report<sup>473</sup> in which a "glyoxime peroxide" structure was assumed). In spite of the fact that the halo compounds are among the longest known furoxan derivatives, their chemistry has received only a cursory study; few spectroscopic and no X-ray diffraction measurements have been made to confirm the structure assignments.

It is reported that dibromofuroxan reacts slowly with diethylamine in ether, to afford a mixture of bisdiethylaminofuroxan and bisdiethylaminoglyoxime.<sup>246</sup> Dioximes are also produced in its reaction with ammonia, hydroxylamine, and aniline; the last reagent is also oxidized to aniline black. Dichlorofuroxan behaves similarly.<sup>83</sup> The dichloro compound rapidly liberates iodine from iodide ion, oxidizes aniline, and forms hygroscopic salts of uncertain composition with aqueous sodium hydroxide, but it does not react with silver nitrite in ether.<sup>83</sup>

On the basis of its reactivity toward iodide ion, which is comparable with that of dichlorofuroxan, the monochlorofuroxan prepared by oxidation of *amphi*-chloroglyoxime (215) was assigned the 3-chloro structure (216). It is a remarkably vigorous oxidizing agent, igniting on charcoal which was being used for its purification.<sup>83</sup> Other monochlorofuroxans, e.g., the methyl<sup>83</sup> and phenyl<sup>473</sup> compounds, which are considerably less reactive, are probably 4-chloro derivatives. The 3-phenyl compound reacts with alcoholic sodium hydroxide to give a mixture of ethoxy- and hydroxy-phenylfuroxan—probably the 3-phenyl derivatives.<sup>473</sup> It is reportedly inert toward aqueous sodium hydroxide, silver nitrate, ammonia, alcoholic hydrazine, boiling aniline, and phosphorus pentachloride.<sup>473</sup> Fewer data are available on the methyl compound: it oxidizes iodide only very slowly, and is decomposed on heating with strong bases.<sup>83,473</sup> The 3-chloro-4-phenyl compound is also known.<sup>107</sup>

## D. FUROXAN SULFIDES AND SULFONES

Some methyl-substituted alkyl- and arylthiofuroxans are known.<sup>95,352</sup> The 4-thio-substituted derivatives are prepared by the action of the appropriate thiolate anion on 3-methyl-4-nitrofuroxan.<sup>95</sup> On heating, they form

<sup>472</sup> I. De Paolini, *Gazz. Chim. Ital.* **60**, 700 (1930).

<sup>473</sup> G. Ponzio, *Gazz. Chim. Ital.* **62**, 127 (1932).

equilibrium mixtures containing appreciable amounts of the 3-thio derivatives.<sup>79</sup> The corresponding sulfones are made by per-acid oxidation of the sulfides.<sup>95,352</sup>

Bisarylsulfonyl and -alkylsulfonyl furoxans can be prepared by nitrosation of sulfonyldiazomethanes,<sup>239,243</sup> from sulfonylacetic acids with nitric acid, and from chloropicrin and an arenesulfinate.<sup>216</sup> In alcohols containing alkali, one (which one is not known) of the sulfonyl groups is replaced by alkoxide.<sup>216</sup>

### E. NITROFUOXANS

Methyl- and phenylnitrofuroxans are the best-studied derivatives of this class, and information on the other members is sparse. The methyl derivative has been prepared and studied by a number of groups.<sup>127,174,286,287</sup> Wieland<sup>288</sup> found that cinnamaldehyde and nitrogen oxides gave a phenylnitrofuroxan, among other products. Both of these are 4-nitro derivatives; the former was established by X-ray crystallography,<sup>51</sup> the latter by its preparation by oxidation of the 4-amino-3-phenyl compound.<sup>471</sup> 3-Nitro-4-phenylfuroxan is produced in small yield by oxidation of 3-amino-4-phenylfuroxan.<sup>471</sup> It is the only 3-nitrofuroxan so far isolated.

Research on the 3-methyl-4-nitrofuroxan is rather hazardous, on account of its tendency to explode unexpectedly. Nucleophilic displacement of the nitro group in 4-nitrofuroxans occurs readily, and it provides a convenient route to a variety of other derivatives.<sup>95,288</sup> Reduction of 4-nitro-3-phenylfuroxan to the amine has been accomplished using stannous chloride.<sup>288</sup> Some nitrofuroxans have been found to liberate iodine from sodium iodide in acetone.<sup>83,446</sup>

### F. HYDROXYFUOXANS AND DERIVATIVES

Hydroxyfuroxans are a practically unknown class. One example—probably the 4-hydroxy-3-phenyl compound—has been reported from the hydrolysis of the nitro<sup>288</sup> and chloro<sup>473</sup> -phenyl compounds. 4-Ethoxy-,<sup>288,473</sup> 4-methoxy-,<sup>95</sup> and 4-phenoxy-<sup>95</sup> furoxans are known, being formed by displacement of 4-chloro or 4-nitro groups in the methyl and phenyl derivatives. Displacement of an arenesulfonyl group has also been found to produce alkoxyfuroxans.<sup>216</sup>

The equilibrium between the 3- and 4-methoxymethylfuroxans lies well in favor of the 4-methoxy compound, which is to a small extent converted into the 3-methoxy derivative on irradiation.<sup>79</sup>

### G. CARBONYL-SUBSTITUTED FUROXANS

Furoxancarboxylic acids are characterized by a more or less ready decomposition, which is probably invariably accompanied by ring cleavage. The derivatives are much more stable. Scheme 12 illustrates a number of the reactions of furoxandicarboxylic acid derivatives. The tendency to nucleophilic addition, followed by ring opening with deacylation, is marked in the diacyl series: some of these reactions were covered in Sections V,C,1 and 2.

#### 1. *Acids*

A furoxanmonocarboxylic acid (222) has been reported by Wieland *et al.*,<sup>464</sup> but it was formed by spontaneous decarboxylation of the dicarboxylic acid (221), and the alternative nitrile oxide formula (223)<sup>465</sup> seems very likely.

Both methylfuroxancarboxylic acids are known.<sup>93</sup> They are considerably more stable than the dicarboxylic acid but are decomposed by heat, particularly the 3-acid (117), the potassium salt of which explodes violently on heating, impact, or friction, when dry.<sup>361</sup> The dry barium and silver furoxan-dicarboxylates are also explosive.<sup>464</sup>

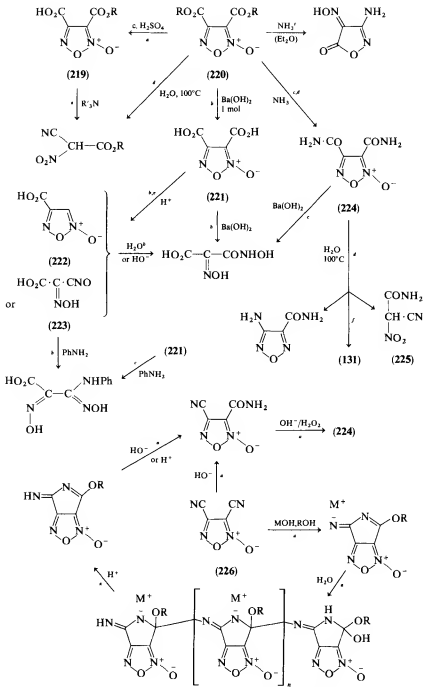
The 4-carboxy group is apparently considerably easier to esterify, and the corresponding ester easier to hydrolyze, than the 3-carboxy; sulfuric acid converts the dimethyl and diethyl esters (220) into 3-alkoxyfuroxan-4-carboxylic acids (219).<sup>372</sup>

#### 2. *Acid Derivatives*

Scheme 12 sets out a number of the transformations observed of the furoxandicarboxylic esters, dicarboxamide (224), and dicyanonitrile (226). Some of the products were found during studies of the chemistry of the cyanilic acids (see Section V,C,2 and Scheme 7). The chemistry of dicyanofuroxan (226) has recently been reinvestigated<sup>372</sup>; in its reactions it shows some similarities to phthalonitrile.

Chlorides, amides, esters, hydrazides, and azides of both of the isomeric methylfuroxancarboxylic acids have been described.<sup>93,94,96,260</sup> The Curtius rearrangement of the azides has received particular attention.<sup>94</sup> The cyano-





<sup>a</sup> Ref. 372. <sup>b</sup> Ref. 464. <sup>c</sup> Ref. 474. <sup>d</sup> Ref. 475. <sup>e</sup> Ref. 465. <sup>f</sup> Ref. 371.

SCHEME 12

methylfuroxan reported in the early literature<sup>476</sup> is a mixture of the two isomers.<sup>79</sup> Cyanophenylfuroxan is stable toward acids but reacts with bases to give ammonia, carbon dioxide, and benzonitrile<sup>477</sup>; its precise structure is unknown.

### 3. Ketones and Ketone Derivatives

Diaroylfuroxans are easily obtained by the action of nitric acid on aryl methyl ketones, or by treating  $\alpha$ -aroyldiazomethanes with a nitrosating agent (see Section IV,A). The best-known member of this series is dibenzoylfuroxan (**231**). The interesting ring transformations that this compound undergoes have already been discussed (Sections V,C,1 and 2). Its degradation reactions are rather involved and have not been completely satisfactorily worked out. Sodium hydroxide is reported simply to produce benzoate ion, while with hydrochloric acid it affords oxalic acid, hydroxylamine, and benzoic acid.<sup>478</sup> It is less extensively broken down by barium hydroxide, with which it forms the barium salt of benzoylmethazonic acid (**227**).<sup>479</sup> Acetic anhydride is reported to form the diacetyl derivative (**228**).<sup>480</sup> Boyer seems to have had some reservations over the latter structure<sup>481</sup>; the former, too, seems rather unexpected.

Some reactions of **231** preserve the furoxan ring. With hydrazine it forms the fused pyridazine **230**, and a number of other diacylfuroxans give analogous products (see Section IV,E). The diketone can be reduced to the diol (**232**) with sodium borohydride,<sup>422</sup> and with diazomethane it forms the bis-epoxide (**233**).<sup>424</sup> With phosphorus pentachloride a benzoyl- $\alpha,\alpha$ -dichlorobenzoylfuroxan is produced.<sup>480</sup> Hydroxylamine and alkali oximate and reduce the ring, forming a tetraoxime (**229**).<sup>482</sup> Scheme 13 summarizes these reactions of dibenzoylfuroxan. Two dioximes of **231** have been described, both produced by dimerization of **120** or via its derivatives<sup>483-485</sup>; their direct formation from **231** and hydroxylamine does not seem to have been recorded.

<sup>474</sup> H. Wieland and E. Gmelin, *Justus Liebigs Ann. Chem.* **367**, 80 (1909); *Ber. Dtsch. Chem. Ges.* **41**, 3512 (1908).

<sup>475</sup> C. Ulpiani, *Gazz. Chim. Ital.* **35**(2), 7 (1905); **42**(1), 209, 243, 375, 390 (1912).

<sup>476</sup> G. Ponzio and G. Bertini, *Gazz. Chim. Ital.* **61**, 51 (1931).

<sup>477</sup> G. Ponzio, *Gazz. Chim. Ital.* **61**, 943 (1931).

<sup>478</sup> A. F. Holleman, *Ber. Dtsch. Chem. Ges.* **21**, 2835 (1888).

<sup>479</sup> E. Durio, *Gazz. Chim. Ital.* **61**, 589 (1931).

<sup>480</sup> G. Ponzio and G. Ruggeri, *Gazz. Chim. Ital.* **56**, 733 (1926).

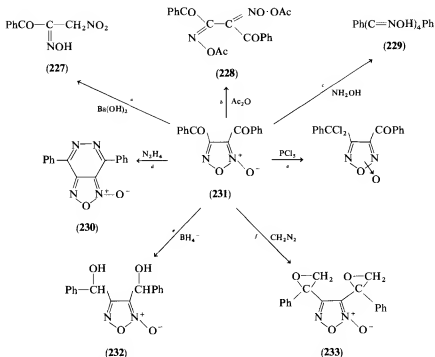
<sup>481</sup> J. H. Boyer, *Heterocycl. Compd.* **7**, 494 (1961).

<sup>482</sup> A. Angeli, *Ber. Dtsch. Chem. Ges.* **26**, 527 (1893).

<sup>483</sup> G. Ponzio and G. Ruggeri, *Gazz. Chim. Ital.* **53**, 708 (1923).

<sup>484</sup> G. Ponzio, *Gazz. Chim. Ital.* **63**, 730 (1933).

<sup>485</sup> G. Ponzio, *Gazz. Chim. Ital.* **66**, 114 (1936).



<sup>a</sup> Ref. 479. <sup>b</sup> Ref. 480. <sup>c</sup> Ref. 482. <sup>d</sup> Ref. 178. <sup>e</sup> Ref. 422. <sup>f</sup> Ref. 424.

SCHEME 13

Diacetylfuroxan, which is described in the older literature as an unstable oil,<sup>172</sup> is considerably more stable when obtained in a reasonably pure state, e.g., prepared as described by Peterson.<sup>173</sup> It is nevertheless prone to explode on distillation. Two dioximes of this compound are also known.<sup>486</sup> Apart from the diaroyl compounds, few other diacetylfuroxans have been reported.<sup>183,214,240,368</sup> The dialdehyde is produced by nitrous acid deoxygenation of  $\alpha$ -isocyanilic acid (144).<sup>487</sup> Otherwise, aldehydes in the furoxan series are unknown. The 3-aldoxime (127) has been found among the fulminic acid derivatives.<sup>371</sup>

A few monoacylfuroxans have been reported. The acetylmethylfuroxan to which a dioxadiazine structure was assigned<sup>488</sup> is in fact the 4-acetyl-3-methyl compound,<sup>348</sup> and the benzoylmethylfuroxan<sup>489</sup> has the benzoyl group in the 4-position.<sup>260</sup> Other members of this class, for instance the

<sup>486</sup> A. Vianello, *Gazz. Chim. Ital.* **62**, 131 (1932).

<sup>487</sup> H. Wieland, *Justus Liebigs Ann. Chem.* **444**, 7 (1925).

<sup>488</sup> G. Tappi, *Gazz. Chim. Ital.* **67**, 388 (1937).

<sup>489</sup> G. Ponzio, *Gazz. Chim. Ital.* **52**(2), 145 (1922).

aminobenzoylfuroxan,<sup>365</sup> are still of uncertain structure. Some cyclic ketones (94, 95, and their 1-oxide isomers) have also been studied.<sup>80</sup>

Of the derivatives of the ketofuroxans, the oximes have received the most attention. That formed from benzoylmethylfuroxan with hydroxylamine hydrochloride (141) undergoes the Beckmann rearrangement to give the methylfuroxan carboxanilide,<sup>260,377</sup> and with dinitrogen tetroxide it forms the  $\alpha,\alpha$ -dinitrobenzyl compound.<sup>377</sup> Its rearrangement in alkali has been discussed in Section V,C,2. The oximes of 4-acetyl-3-methylfuroxan<sup>488</sup> and acetylphenylfuroxan<sup>490</sup> behave similarly with dinitrogen tetroxide, but they are unaltered by base.

The early work on the oxidation products of the dioximes of the diketones (32) and their rearrangements in acid and alkali were summarized by Boyer.<sup>4</sup> The area is still in need of a thorough reinvestigation, to correct the structures of a number of fused-ring products (e.g., 31), and to settle the many outstanding questions of oxime configuration and furoxan ring isomerism which remain.

### VIII. Benzofuroxans: Reactions at the Homocyclic Ring

In the decade since the previous review<sup>6</sup> there have been a number of developments in the study of the interaction of nucleophilic reagents with benzofuroxans, but little, apart from routine nitrations and halogenations, on the reactions of electrophiles or other species.

Compounds with activated halogen atoms, e.g., 7-chloro-4-nitrobenzofuroxan (234), undergo displacement reactions with a variety of nucleophiles, including sulfides,<sup>300,443,444</sup> amines,<sup>300,443,491</sup> phenoxides,<sup>300</sup> and others mentioned earlier.<sup>6</sup> Sometimes rearrangements of the type discussed in Section V,C,4 occur, leading to products other than those of simple displacement.<sup>300,443</sup> When 7-chloro-4-nitrobenzofuroxan is treated with an arylsulfinate, both substituents are replaced, and the 4,7-bisarylsulfonyl compound is formed. One of the arylsulfonyl groups is, in its turn, susceptible to replacement by other nucleophiles.<sup>444</sup>

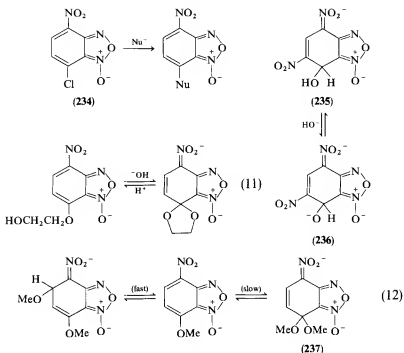
In the absence of a leaving group, several well-defined reactions may still occur. The adducts (235) of 4,6-dinitrobenzofuroxan with hydroxide ion have long been known, and have received further study on account of their explosive properties: the barium<sup>492</sup> and potassium<sup>493</sup> salts are the subjects

<sup>490</sup> G. Ponzio and G. Tappi, *Gazz. Chim. Ital.* **67**, 518 (1937).

<sup>491</sup> J. G. Belton, M. L. Conalty, and J. F. O'Sullivan, *Proc. R. Ir. Acad.* **76B**, 133 (1976) [*CA* **86**, 83521 (1977)].

<sup>492</sup> T. Piechowicz, South African Patent 68/00,982 (1968) [*CA* **70**, 69768 (1969)]; French Patent 1,522,297 (1969) [*CA* **71**, 5034 (1969)].

<sup>493</sup> T. Piechowicz, French Patent 1,519,799 (1968) [*CA* **71**, 31970 (1969)].



of patents. A second proton can be removed by further alkali; at pH above 10.6 the dianion **236** is produced.<sup>494</sup>

The kinetics and equilibria of the reaction of 4,6-dinitrobenzofuroxan with water (forming **235**),<sup>494-496</sup> and of the cyclization of 7-(hydroxyethoxy)-4-nitrobenzofuroxan with alkali, in water and in dimethyl sulfoxide (Eq. 11)<sup>497</sup> have received detailed study. Proton NMR spectroscopy has shown that methoxide ions add more quickly to the 5-position of 7-methoxy-4-nitrobenzofuroxan, but the "thermodynamic product" is the 7,7-dimethoxy adduct (**237**) (Eq. 12).<sup>498</sup> Methoxide adducts are also formed with 4-nitrobenzofuroxan.<sup>499</sup> The impetus for much of this work was provided by the suggestion that antitumor and antileukemic properties which have been observed in some benzofuroxans might be connected with their ability to form Meisenheimer complexes of the types illustrated in this section.<sup>300,416,500</sup>

<sup>494</sup> F. Terrier, F. Millot, and W. P. Norris, *J. Am. Chem. Soc.* **98**, 5883 (1976).

<sup>495</sup> F. Terrier, F. Millot, and W. P. Norris, *Bull. Soc. Chim. Fr.*, 551 (1975).

<sup>496</sup> G. Ah-Kow, *C. R. Acad. Sci., Ser. C* **287**, 231 (1978).

<sup>497</sup> G. Ah-Kow, F. Terrier, and F. Lessard, *J. Org. Chem.* **43**, 3578 (1978).

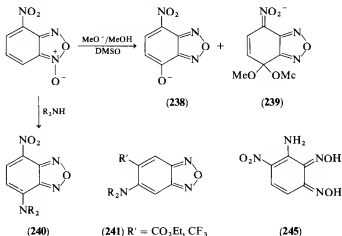
<sup>498</sup> E. Buncel, N. Chuaqui-Offermanns, and A. R. Norris, *J. C. S. Perkin I*, 415 (1977).

<sup>499</sup> F. Terrier, F. Millot, A. P. Chatrousse, M. J. Pouet, and M. P. Simonnin, *Org. Magn. Reson.* **8**, 56 (1976); F. Terrier, A. P. Chatrousse, and F. Millot, *J. Org. Chem.* **45**, 2666 (1980).

<sup>500</sup> M. W. Whitehouse and P. B. Ghosh, *Biochem. Pharmacol.* **17**, 158 (1968).

Hydroxide ion replaces the methoxide of 7-methoxy-4-nitrobenzofuroxan to form the 7-hydroxy-4-nitro compound, which rearranges to the 5-hydroxy-4-nitro derivative, under certain conditions.<sup>418</sup> Buncel *et al.*<sup>501</sup> have also described the demethylation of 7-methoxy-4,6-dinitrobenzofuroxan by methoxide ion.

Several groups have reported reactions of nitrobenzofuroxans in basic media which result in benzene ring substitution with concomitant reduction of the furoxan part. 4-Nitrobenzofuroxan with methoxide in dimethyl sulfoxide forms the benzofurazan anions **238** and **239**.<sup>502</sup> Dialkylamines react similarly, producing aminofurazans (**240**).<sup>452</sup> The 5-trifluoromethyl and 5-ethoxycarbonyl benzofuroxans are reported to form 6-amino-substituted benzofurazans (**241**).<sup>451</sup> Cyclohexylamine reacts with the quinone **242**, giving a mixture of the amino- and diaminofurazan quinones **243** and **244**.<sup>503</sup> With other nucleophiles *o*-quinone dioximes are produced. Hydroxylamine reacts with 2,4-dinitrochlorobenzene, and with *N*-(2,4-dinitrophenyl) amino acids, giving **245**. The authors suggest that 5-nitrobenzofuroxan is an intermediate, which is substituted and further reduced by more hydroxylamine.<sup>504</sup> The reaction of thiols with benzofuroxan is proposed to occur by attack of thiolate at C(6), and then a second thiol attacks the first sulfur group (**246**), giving  $R_2S_2$  and forming *o*-benzoquinone dioxime.<sup>438,439</sup>

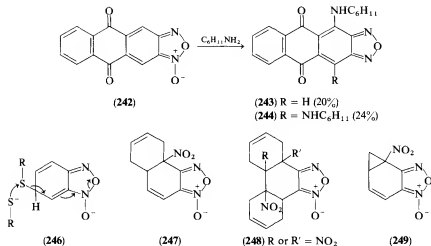


<sup>501</sup> E. Buncel, N. Chuaqui-Offermans, R. Y. Moir, and A. R. Norris, *Can. J. Chem.* **57**, 494 (1979).

<sup>502</sup> E. Buncel, N. Chuaqui-Offermans, B. K. Hunter, and A. R. Norris, *Can. J. Chem.* **55**, 2852 (1977).

<sup>503</sup> M. V. Gorelik and V. I. Lomzakova, *Khim. Geterotsikl. Soedin.*, 1275 (1974) [*CA* **82**, 16755 (1975)].

<sup>504</sup> M. Hasegawa, Y. Uchino, M. Satomi, and T. Okamoto, *Yakugaku Zasshi* **95**, 147 (1975) [*CA* **83**, 10766 (1959)].



Butadiene reacts with 4-nitrobenzofuroxan to give a 1:1 adduct, **247**, and with the 4,6- and 5,6-dinitro compounds it forms 2:1 adducts **248**. Isoprene and 2,3-dimethylbutadiene react similarly. The authors pointed out that no products of addition to the nitroso groups of the ring-opened *o*-dinitroso-benzene derivative could be found.<sup>340</sup>

Diazomethane and 4-nitrobenzofuroxan react, with loss of nitrogen, to form the cyclopropa-fused derivative **249** (20%), along with a considerable amount of unidentified material.<sup>505</sup>

## IX. Uses

### A. FUROXANS IN ORGANIC SYNTHESIS

The conversion of benzofuroxans into quinoxaline di-*N*-oxides (Section V,C,3) provides a quick and easy route to this class of compound, and considerable effort has been expended in the search for a medicinally valuable product. The dioxides show strong antibacterial activity, but it appears that, in the range of compounds investigated so far, the margin between effectiveness toward bacteria and toxicity toward mammals is too small to allow their use in human medicine. However, 2-(acetoxymethoxycarbonyl)-3-methylquinoxaline dioxide<sup>506,507</sup> and the methoxycarbonylhydrazone of

<sup>505</sup> R. C. Boruah, P. Devi, and J. S. Sandhu, *J. Heterocycl. Chem.* **16**, 1555 (1979).

<sup>506</sup> T. H. Cronin and K. Richardson, Ger. Offen. 2,215,231 (1972) [*CA* **78**, 72208 (1973)]; R. V. Kasubick and R. L. Robertson, Fr. Demande 2,132,378 (1972) [*CA* **78**, 159673 (1973)].

<sup>507</sup> T. H. Cronin and K. Richardson, U.S. Patent 4,007,184 (1977) [*CA* **86**, 190008 (1977)].

the 2-aldehyde (Carbadox, Mecadox)<sup>508</sup> have been recommended as animal feed additives, particularly for encouraging the growth of pigs. Many patents<sup>509</sup> have been filed concerned with the synthesis of intermediates in the preparation of the latter product. The Beirut reaction was also used to convert 5,6-dimethylbenzofuroxan into a key intermediate in a synthesis of lumichrome.<sup>510</sup> The preparation of 3-amino-1,2,4-benzotriazine and benzimidazole oxides is also described in Section V,C,3; the route through benzofuroxans provides the most convenient means of access to these substances.

Strained furoxans are exploited as a source of polymer intermediates, since on mild heating they ring-open to dinitrile dioxides, which undergo spontaneous or catalyzed rearrangement to diisocyanates.<sup>76,332</sup> Unstrained furoxans are also useful sources of nitrile oxides, which they provide on flash vacuum pyrolysis,<sup>334</sup> or isocyanates, if the nitrile oxides are allowed to rearrange<sup>333,511</sup> (Section V,A).

The reduction of furoxans by lithium aluminum hydride to give amines,<sup>182,283,423,424</sup> and of fused furoxans to diamines<sup>283,423</sup> (Section V,D), has potential utility; ring cleavages brought about by this reaction show a number of synthetic possibilities. The catalytic hydrogenation of tetrahydrobenzofuroxan to hexamethylenediamine is also potentially useful.<sup>279,420</sup> *o*-Benzoquinone dioxime may be prepared very easily by reduction of benzofuroxan (Section V,D,5).

Nitriles and dinitriles are also valuable intermediates, and their preparation by phosphite deoxygenation of furoxans (Section V,D,3) opens further routes via these compounds. It has been suggested<sup>512</sup> that methyl groups may be modified, by alkylation, condensation, etc., before deoxygenation;

<sup>508</sup> See, e.g. V. Russo, A. Catelano, and S. Vitali, *Atti Soc. Ital. Sci. Vet.* **22**, 354 (1968) [*CA* **71**, 47137 (1969)]; G. W. Thrasher, J. E. Shively, C. E. Askelson, W. E. Babcock, and R. R. Chalquest, *J. Anim. Sci.* **28**, 208 (1969) [*CA* **70**, 75593 (1969)]; **31**, 333 (1970) [*CA* **73**, 74402 (1970)]; V. Dzapo and H. Reuter, *Arch. Tierernaehr.* **22**, 615 (1972) [*CA* **78**, 70577 (1973)]; J. P. Raynaud and H. Bretheau, *Rev. Med. Vet.* **124**, 375 (1973) [*CA* **79**, 13629 (1973)].

<sup>509</sup> See, e.g., J. D. Johnston (C. Pfizer and Co.), Belgian Patent 669,353 (1964); U.S. Patents 3,371,090 (1968), 3,433,871 (1969) [*CA* **65**, 7196 (1966)]; Ger. Offen. 1,927,337 (1970) [*CA* **72**, 100753 (1970)]; J. Dukai, M. Barath, and A. Kelemen, Ger. Offen. 2,423,093 (1974) [*CA* **83**, 164229 (1975)]; P. Benko, I. Simonek, L. Pallos, L. Buda, P. Foris, J. Kovacs, and K. Magyar, Ger. Offen. 2,527,157 (1976) [*CA* **84**, 180291 (1976)]; J. Lojka, B. Doubrava, L. Novacek, J. Belusa, and L. Bohuminsky, Czech Patent 167,695 (1977) [*CA* **88**, 50923 (1978)]; J. Belusa, M. Holik, R. Kulka, and L. Novacek, *Chem. Zvesti* **32**, 232 (1978) [*CA* **89**, 179144 (1978)].

<sup>510</sup> F. Seng and K. Ley, *Angew. Chem., Int. Ed. Engl.* **11**, 1010 (1972).

<sup>511</sup> J. Crosby, R. M. Paton, and R. A. C. Rennie, German Patent 2,336,403 (1974) [*CA* **81**, 49257 (1974)].

<sup>512</sup> A. I. Meyers, "Heterocycles in Organic Synthesis," p. 298. Wiley (Interscience), New York 1974.



however, for this to succeed a way has first to be found to circumvent the base-induced Angeli rearrangement described in Section V,C,1.

## B. BIOLOGICAL PROPERTIES AND APPLICATIONS OF FUROXANS

Wide-ranging biological activity has been claimed for furoxan and benzofuroxan derivatives. Some are depressants of the central nervous system,<sup>469</sup> or of frog flexor muscle reflexes,<sup>513</sup> or are reported as muscle-relaxants and anticonvulsants.<sup>469</sup> Vasodilatory activity has been noted in some fused benzofuroxan derivatives.<sup>309</sup> Nematocidal,<sup>514</sup> antimicrobial,<sup>280,352,446,514,515</sup> (modest) fungicidal,<sup>516</sup> herbicidal,<sup>517</sup> algicidal,<sup>518</sup> and plant growth regulatory<sup>519</sup> activities are listed. Some semisynthetic penicillins containing the furoxan ring have been tested for antibacterial activity.<sup>520</sup>

Nitrobenzofuroxans, pyridofuroxan, and some fused benzofuroxans have been found to inhibit nucleic acid<sup>300,313,416,500,521</sup> and protein<sup>313</sup> synthesis in leukocytes. Some of these compounds show particular activity against leukemia<sup>300,313,521</sup> and other forms of cancer cells<sup>522</sup>; their mode of action has been discussed.<sup>300</sup> Some anticancer-active benzofuroxans were tested for mutagenicity in *Salmonella* organisms.<sup>523,524</sup> The inhibition of rat liver mitochondrial monoamine oxidase activity has been found.<sup>525</sup> Some furoxans have been investigated as radioprotectants.<sup>526</sup> A fuller account of the biological properties of benzofuroxans is recently published.<sup>527</sup>

<sup>513</sup> A. Fundaro, *Boll. Soc. Ital. Biol. Sper.* **50**, 1650, 1654 (1974); A. Fundaro and M. C. Cassone, *Farmaco, Ed. Sci.* **30**, 891 (1975); *Pharmacol. Res. Commun.* **8**, 253 (1976).

<sup>514</sup> J. T. Hackman and J. Kuipers, German Patent 2,135,920 (1972) [*CA* **76**, 149985 (1972)].

<sup>515</sup> M. A. Bianco, *Atti Accad. Sci. Torino, Cl. Sci. Fis., Mat. Nat.* **108**, 479 (1974).

<sup>516</sup> A. Gasco, V. Mortarini, A. Serafino, R. Calvino, E. Menziani, and E. Reynaud, *Farmaco, Ed. Sci.* **30**, 900 (1975).

<sup>517</sup> R. Iwamoto, H. Sakata, K. Okumura, A. Hongo, and S. Sekiguchi, Japanese Patent 77/07, 055 [*CA* **87**, 128883 (1977)].

<sup>518</sup> H. Koopman and J. Daams, *Weed Res.* **5**, 319 (1965) [*CA* **64**, 10339 (1966)].

<sup>519</sup> W. N. Cannon and K. Gerzon, U.S. Patent 3,420,654 (1969) [*CA* **70**, 87818 (1969)].

<sup>520</sup> K. L. Hill, South African Patent 6,804,716 (1968) [*CA* **71**, 61392 (1969)].

<sup>521</sup> D. Kessel and J. G. Belton, *Cancer Res.* **35**, 3735 (1975) [*CA* **84**, 53782 (1976)].

<sup>522</sup> V. C. Barry, J. G. Belton, and M. L. Conalty, *Chemother., Proc. Int. Congr. Chemother.* **9th**, 1975, **8**, 97 (1976) [*CA* **86**, 182 960 (1977)].

<sup>523</sup> S. Thompson and L. Kellicut, *Mutat. Res.* **48**, 145 (1977) [*CA* **86**, 183026 (1977)].

<sup>524</sup> D. G. Macphree, G. P. Roberts, B. Ternai, P. B. Ghosh, and R. Stephens, *Chem.-Biol. Interact.* **19**, 77 (1977) [*CA* **88**, 58253 (1978)].

<sup>525</sup> A. G. Bolt, P. B. Ghosh, and M. J. Sleight, *Biochem. Pharmacol.* **23**, 1963 (1974) [*CA* **82**, 27802 (1975)].

<sup>526</sup> T. J. Haley, A. M. Flesher, and L. Mavis, *Nature (London)* **195**, 1012 (1962); *Arch. Int. Pharmacodyn. Ther.* **138**, 133 (1962).

<sup>527</sup> P. B. Ghosh, B. Ternai, and M. W. Whitehouse, *Med. Res. Rev.* **2**, 158 (1981).

Furoxans have been recommended for use as accelerators of sensitized photographic emulsions,<sup>528</sup> and as oxidants in color formers.<sup>529</sup> Benzofuroxan, when added to photopolymerizable printed circuit compositions, is said to improve the definition of the image.<sup>530</sup> It is also beneficial as a constituent of carbon paper coatings.<sup>531</sup> Some substituted benzofuroxans are proposed as inhibitors of styrene polymerization,<sup>532</sup> and other furoxans suppress the formation of films on drying oils.<sup>280</sup>

Several metallurgical and electrochemical applications have been suggested for benzofuroxans. They have been included in aluminum polishing solutions<sup>533</sup> and steel corrosion inhibitors,<sup>534</sup> and as depolarizers in aqueous and nonaqueous electric cells.<sup>435,436</sup>

In the field of propellants and explosives, studies have been made of the detonation properties of "potassium dinitrobenzofuroxan"<sup>493,535</sup> and the corresponding barium salt,<sup>492</sup> of 3-methyl-4-nitrofuroxan,<sup>127</sup> of benzo-trifuroxan,<sup>129,130</sup> and of dicyanofuroxan.<sup>128,134</sup> This last compound is used in preparing a hypergolic bipropellant system,<sup>536</sup> and as a constituent, with tetrazole polymers, of solid fuels for rocket propulsion.<sup>537</sup>

Benzofuroxan has been proposed for use as a biochemical assay of enzymic thiol groups,<sup>438</sup> and as a spot test for malononitrile and its derivatives, with which it forms a violet color in the presence of alkali.<sup>538</sup>

## X. Appendix

$\alpha$ -Ethyneyl acetates have been found to be converted into diacylfuroxans [**24**; R = R'<sub>2</sub>C(OAc)-CO] by nitrosyl fluoride and nitrosonium tetrafluoroborate, or by nitronium tetrafluoroborate. Nitroacetylenes are suggested to be intermediates. Other terminal acetylenes were tried unsuccessfully in the

<sup>528</sup> E. Wainer and J. E. Shirey, U.S. Patent 3,481,739 (1969) [CA 72, 37727 (1970)].

<sup>529</sup> S. J. Ciarca and A. T. Brault, Fr. Demande 2,232,777 (1975) [CA 84, 67800 (1976)].

<sup>530</sup> G. R. Nalli and J. F. Pazos (E. I. du Pont de Nemours and Co.), Ger. Offen. 2,533,073 (1976) [CA 86, 180729 (1977)]; Fr. Demandes 2,299,666, 2,307,823 (1976) [CA 86, 163360 (1977); CA 87, 203180 (1977)]; British Patent 1,481,397 (1977) [CA 88, 43761 (1978)].

<sup>531</sup> J. F. McKellar and G. G. Warburton, British Patent 1,395,336 (1975) [CA 83, 133634 (1975)].

<sup>532</sup> H. Shimizu, T. Arai, and S. Harada, Japan. Kokai 77/102231, 77/133931 [CA 88, 62733, 90234 (1978)].

<sup>533</sup> T. R. Rooney, Ger. Offen. 2,647,315 (1977) [CA 87, 105688 (1977)].

<sup>534</sup> W. Costain and B. W. H. Terry, Ger. Offen. 2,147,847 (1972) [CA 77, 82988 (1972)].

<sup>535</sup> R. H. Homewood, V. J. Krukons, and R. C. Loszewski, U.S. Patent 3,832,249 (1974) [CA 82, 113795 (1975)].

<sup>536</sup> D. D. Denson and F. M. Van Meter, U.S. Patent 3,740,947 (1973) [CA 79, 94195 (1973)].

<sup>537</sup> W. R. Carpenter, U.S. Patent 3,386,968 (1968) [CA 69, 28 106 (1968)].

<sup>538</sup> M. J. Haddadin, U. Khalidi, N. Turjuman, and R. Ghougassian, *Anal. Chem.* **46**, 2072 (1974).

reaction.<sup>539</sup> Some of these diacylfuroxans apparently dissociate to the monomeric nitrile oxides  $R'_2C(OAc) \cdot CO \cdot CNO$ , as shown by their trapping to form adducts with various dipolarophiles. Another reaction, which was more generally observed with diacylfuroxans including the dibenzoyl compound (**114**; Ar = Ph), was the production of adducts of type **116**. The authors also report that dibenzoylfuroxan forms the "tetramer" structure **29** when refluxed in toluene, and they suggest that **116** was not formed as indicated in Scheme 5, but instead a nitrile oxide,  $PhCO \cdot C(:NOCOPh) \cdot CNO$ , was produced by rearrangement of the half-cleaved diacylfuroxan ( $74 \rightleftharpoons 23$ ) with migration of an acyl group from C to O in the trans isomer (**23**; R = PhCO).<sup>540</sup>

Soviet workers have reinvestigated the phenylfuroxan isomers<sup>541</sup>; their results seem to be in agreement with those of Ponzio<sup>380,457</sup> and Burakevich *et al.*,<sup>362</sup> summarized in Section VI. Theoretical calculations (MINDO) on furoxan electron configuration, and on their equilibrium constants (cf. Section V,B) have been made,<sup>542</sup> but the full details are not yet available to us.

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<sup>539</sup> D. R. Brittelli and G. A. Boswell, *J. Org. Chem.* **46**, 312 (1981).

<sup>540</sup> D. R. Brittelli and G. A. Boswell, *J. Org. Chem.* **46**, 316 (1981).

<sup>541</sup> L. I. Khmel'nitskii, T. I. Godovikova, N. A. Ruleva, B. N. Khasapov, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2295 (1979) [*CA* **92**, 94317 (1980)].

<sup>542</sup> M. A. Shokhen, *Sint. Issled. Biol. Soedin., Tezisy Dokl. Konf. Molodykh Uch.*, 6th, 17 (1978) [*CA* **92**, 180522 (1980)].

# The Chemistry of the Isoindoles

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## I. Introduction

In contrast to the indoles, the isoindoles appeared late on the chemical scene. Early attempts to prepare isoindole (1) or its simple derivatives were unsuccessful,<sup>1-3</sup> and these substances did not become known until 1951 when Wittig and his colleagues obtained 2-methylisoindole.<sup>4</sup>



(1) Isoindole  
(2*H*-Isoindole)



(2) 1*H*-Isoindole  
(Isoindolenine)



(3) Isoindoline

The isoindoles were reviewed in this series by White and Mann in 1969.<sup>5</sup> Since that time there has been a considerable expansion in isoindole chemistry, including, in 1972, the isolation and characterization of the parent system.<sup>6</sup> The present review concentrates on developments since 1969, but a certain amount of chemistry from earlier years is included where appropriate. Throughout, the use of the name isoindole in a general context does not imply the absence of the 1*H*-isoindole (isoindolenine) tautomer (2) if

<sup>1</sup> S. Gabriel and A. Neumann, *Ber. Dtsch. Chem. Ges.* **26**, 705 (1893).

<sup>2</sup> J. Malan and R. Robinson, *J. Chem. Soc.*, 2653 (1927).

<sup>3</sup> G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 3295 (1928).

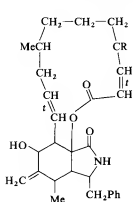
<sup>4</sup> G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Justus Liebigs Ann. Chem.* **572**, 1 (1951).

<sup>5</sup> J. D. White and M. E. Mann, *Adv. Heterocycl. Chem.* **10**, 113 (1969).

<sup>6</sup> R. Bonnett and R. F. C. Brown, *Chem. Commun.*, 393 (1972); R. Bonnett, R. F. C. Brown, and R. G. Smith, *J. C. S. Perkin I*, 1432 (1973).

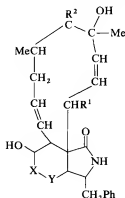
this is structurally possible. Tautomerism is specifically considered in Section V.B.

Isoindoles are not known to occur as natural products; again, there is a marked contrast with the indoles. However, the cytochalasins, a group of mold metabolites having a marked effect on cell division, contain a highly substituted isoindoline nucleus (3). Cytochalasins A and B (4 and 5) have been obtained from *Helminthosporium dematioides*,<sup>7</sup> cytochalasins C and D (6 and 7) from *Metarrhizium anisopliae*,<sup>8</sup> and the cytochalasins 8 and 9 from the fungus *Phomopsis paspalli* found on an Indian millet.<sup>9</sup>



(4) R = O

(5) R = H, OH



(6)  $\text{X}-\text{Y} = \text{MeC}=\text{CMe}$ ,  $\text{R}^1 = \text{OAc}$ ,  $\text{R}^2 = \text{O}$

(7)  $\text{X}-\text{Y} = \text{CH}_2=\text{C}-\text{CHMe}$ ,  $\text{R}^1 = \text{OAc}$ ,  $\text{R}^2 = \text{O}$

(8)  $\text{X}-\text{Y} = \text{CH}_2=\text{C}-\text{CHMe}$ ,  $\text{R}^1 = \text{OAc}$ ,  $\text{R}^2 = \text{H}_2$

(9)  $\text{X}-\text{Y} = \text{CH}_2=\text{C}-\text{CHMe}$ ,  $\text{R}^1 = \text{OH}$ ,  $\text{R}^2 = \text{H}_2$

## II. The Parent System

### A. SYNTHESIS

Indole was prepared by Baeyer in 1866<sup>10</sup>; isoindole did not appear until 1972, when three groups in swift succession obtained it by independent routes. Fenton and Ingold<sup>3</sup> had attempted in 1928 to eliminate toluene-sulfinic acid from 2-tosylisoindoline, but hydrolysis had prevailed. Some

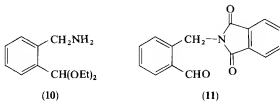
<sup>7</sup> D. C. Aldridge, J. J. Armstrong, R. N. Speake, and W. B. Turner, *J. Chem. Soc. C*, 1667 (1967); cf. S. B. Carter, *Nature (London)* **213**, 261 (1967).

<sup>8</sup> D. C. Aldridge and W. B. Turner, *J. Chem. Soc. C*, 923 (1969).

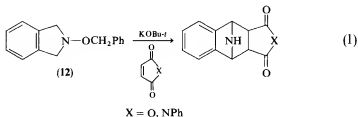
<sup>9</sup> S. A. Patwardhan, R. C. Pandey, S. Dev, and G. S. Pendse, *Phytochemistry* **13**, 1985 (1974).

<sup>10</sup> A. Baeyer, *Justus Liebigs Ann. Chem.* **140**, 295 (1866).

years later, cyclization procedures that were satisfactory with substituted derivatives were tried unsuccessfully. Thus the acid-catalyzed cyclization of the aminoacetal **10** gave only reddish-violet resins,<sup>11</sup> while the hydrazinolysis of **11**, the aminoaldehyde protected at the alternative site, gave polymeric material.<sup>12</sup>



The formation of dark-colored polymeric material, such as has been observed also on the electrochemical reduction of 1,2-dihydropthalazine<sup>13</sup> and on treating 2-tosylisoindoline with potassium *t*-butoxide,<sup>6</sup> might reasonably have been taken as a signal that isoindole had been formed and was a very reactive substance. The trapping of isoindole produced by the base-promoted elimination of benzyl alcohol from 2-benzyloxyisoindoline (**12**) was more definitive (Eq. 1)<sup>14</sup>: it showed that isoindole was formed, although spectroscopic characterization of the intermediate was still not possible.



In 1972, Bonnett and Brown reported the first successful isolation of isoindole using a gas-phase pyrolysis technique.<sup>6</sup> 2-Methoxycarbonyloxyisoindoline (**13**) was sublimed at 0.01 mm Hg through a silica tube at 500°C, and isoindole was collected on a target at ~77K (Eq. 2 and Fig. 1). The isoindole so formed was a white solid that rapidly darkened and resinified at room temperature. Although combustion analysis could not be obtained, the accurately measured molecular ion ( $M^+ = 117.0576$ ) agreed with the molecular formula ( $C_8H_7N$  requires 117.0578). The <sup>1</sup>H-NMR

<sup>11</sup> J. Bornstein, S. F. Bedell, P. E. Drummond, and C. L. Kosloski, *J. Am. Chem. Soc.* **78**, 83 (1956).

<sup>12</sup> D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.* **86**, 4152 (1964).

<sup>13</sup> H. Lund and E. T. Jensen, *Acta Chem. Scand.* **24**, 1867 (1970).

<sup>14</sup> R. Kreher and J. Seubert, *Z. Naturforsch., Teil B* **20**, 75 (1965).

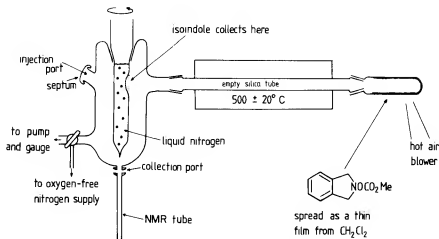
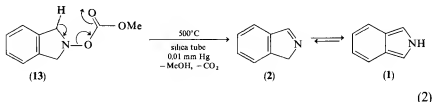
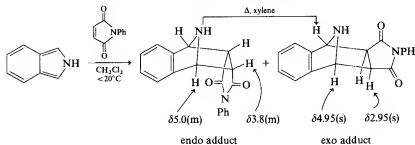


FIG. 1. Apparatus employed for the preparation of isindole by the gas-phase flash pyrolysis of 2-methoxycarbonyloxyisindoline.<sup>6</sup> The isindole collects on the cold target and, as the coolant evaporates, may be washed off with a suitable solvent and collected (e.g., for NMR study). (Adapted from Bonnett and Brown<sup>6</sup> with the permission of the publishers.)



spectrum in  $[^2\text{H}_6]\text{acetone}$  (Fig. 2), the infrared spectrum ( $3350, 740\text{ cm}^{-1}$ ), and the electronic spectrum (Fig. 3) were recorded and interpreted in terms of the isindole structure. Reaction with *N*-phenylmaleimide gave a mixture of the endo and exo adducts (Eq. 3), the former isomer being converted to the latter under equilibrating conditions (xylene, reflux).





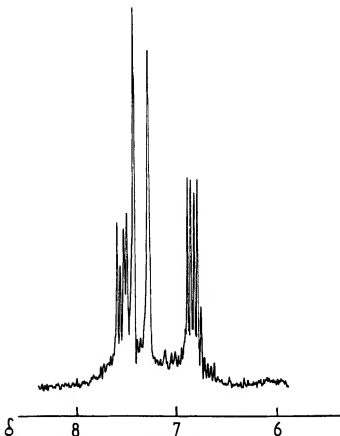
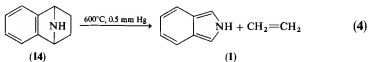


FIG. 2.  $^1\text{H}$ -Nuclear magnetic resonance spectrum of isoindole in  $[\text{}^2\text{H}_6]\text{acetone}$  (100 MHz,  $0^\circ\text{C}$ , trace  $\text{D}_2\text{O}-\text{Et}_3\text{N}$ ). (From Bonnett and Brown<sup>6</sup> with the permission of the publishers.)

Shortly after this report, two other routes to isoindole were announced. Both involved retro-Diels-Alder reactions. The first, carried out by Bornstein and his colleagues,<sup>15</sup> employed the gas-phase pyrolysis of **14** to give isoindole and ethylene (Eq. 4). This approach has been developed further by employing the *N*-*t*-butoxycarbonyl derivative (Section III,B).<sup>16</sup>



<sup>15</sup> J. Bornstein, D. E. Remy, and J. E. Shields, *Chem. Commun.*, 1149 (1972).

<sup>16</sup> E. Chacko, J. Bornstein, and D. J. Sardella, *Tetrahedron* **35**, 1055 (1979).

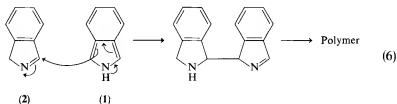


conditions.<sup>17</sup> The isoindole (**1**) was separated from 3,6-dipyridylpyridazine (**16**) by sublimation of the former at about room temperature.

Isoindole has been detected (by trapping it with *N*-phenylmaleimide) in the pyrolysis of 1-phenyl-1,2,4-triazole at 800°C (Section III.F).<sup>18</sup>

## B. PROPERTIES

Isoindole is a white solid which becomes discolored and resinous at room temperature, especially in the presence of air. It may be handled for short periods using vacuum techniques, or in solution under an inert atmosphere. The instability has been attributed to a self-condensation (Eq. 6) analogous to that shown by pyrrole under acidic conditions.<sup>6,19</sup>



The <sup>1</sup>H-NMR spectrum (Fig. 2) shows isoindole to be aromatic on the induced ring current criterion, the principal features of the spectrum being AA'BB' multiplets at  $\delta$ 7.5 (H-4, H-7) and  $\delta$ 6.8 (H-5, H-6) and a broad singlet at  $\delta$ 7.38 (H-1, H-3)<sup>6</sup>. The NH proton (exchangeable, D<sub>2</sub>O-Et<sub>3</sub>N) occurs as a broad signal at about  $\delta$ 10.<sup>20</sup> The isoindole tautomer (**1**) predominates, but a small equilibrium concentration of the isoindolenine (**2**) is presumably present. The isoindolenine has been detected in the product from the pyrolysis of **14** (Eq. 4), where it appears to be formed in a non-equilibrium concentration.<sup>20</sup> The NMR spectrum of a sample in CDCl<sub>3</sub> at -40°C shows signals at  $\delta$ 8.65 (t,  $J = 3$  Hz, 3-H) and at  $\delta$ 4.87 (d,  $J = 3$  Hz, 1-H<sub>2</sub>) attributed to **2**. These signals gradually disappear, while the signals attributed to isoindole (**1**) increase in intensity.

The electronic spectrum of isoindole (Fig. 3) in hexane possesses considerable vibrational fine structure ( $\lambda_{\max}$  306.5, 312.5, 320, 326.5, and 335 nm). The spectra of 2-alkylisoindoles and of isobenzofuran are rather similar.<sup>6,21</sup>

<sup>17</sup> G. M. Priestley and R. N. Warrener, *Tetrahedron Lett.*, 4295 (1972).

<sup>18</sup> T. L. Gilchrist, C. W. Rees, and C. Thomas, *J. C. S. Perkin I*, 12 (1975).

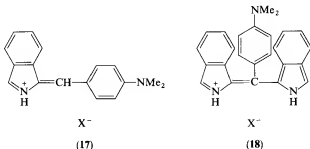
<sup>19</sup> H. A. Potts and G. F. Smith, *J. Chem. Soc.*, 4018 (1957).

<sup>20</sup> E. Chacko, J. Bornstein, and D. J. Sardella, *Tetrahedron Lett.*, 1095 (1977).

<sup>21</sup> R. N. Warrener, *J. Am. Chem. Soc.*, **93**, 2346 (1971); D. Wege, *Tetrahedron Lett.*, 2337 (1971).

The isindole solution emits a greenish blue fluorescence in ultraviolet light (medium pressure Hg). The mass spectrum (electron impact) shows a strong molecular ion, with important fragments at  $m/e$  90 ( $M - \text{HCN}$ )<sup>+</sup>, 89 ( $M - \text{HCN} - \text{H}$ )<sup>+</sup>, and 63 ( $\text{C}_5\text{H}_3$ )<sup>+</sup>.<sup>6,22</sup>

Isindole reacts with ethanolic 1,3,5-trinitrobenzene to give a deep red color attributed to a  $\pi$ -complex. With Ehrlich's reagent a red-purple color, which slowly turns blue, is observed. This reaction presumably involves electrophilic substitution at C-1 (Section V,D) to give charge resonance systems of the types shown in **17** and **18** (cf. Section V,F,2).

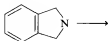


Diels-Alder reactions of isindole give crystalline products which are easily handled. The reaction with *N*-phenylmaleimide is outlined in Eq. (3). Adducts with maleic anhydride and with *N*-methylmaleimide have also been obtained.<sup>14,15,17</sup>

### III. Synthesis of Isoindoles

Syntheses of *N*-substituted isindoles predominate. In general, these compounds (which are not, of course, tautomeric systems) are more easily prepared and manipulated than are the isindoles which have no substituent at nitrogen. All reactions in this series should be carried out in an inert atmosphere.

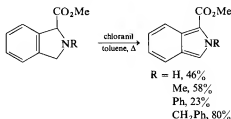
#### A. SYNTHESSES FROM ISOINDOLINES



<sup>22</sup> R. G. Smith, Ph.D. Thesis, London (1970).

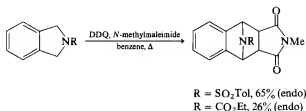
### 1. Dehydrogenation

Where a strongly electron-withdrawing substituent is present at C-1 or C-3, the isoindolines can be conveniently dehydrogenated with a high-potential quinone.<sup>23</sup> 1,3-Dimethoxycarbonylisoindoles have been prepared



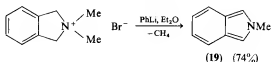
in an analogous manner.<sup>24</sup>

Dehydrogenation of 2-tosyl- and 2-ethoxycarbonylisoindolines has also been observed; in this case it is necessary to trap the intermediate isoindole with a dienophile.<sup>25</sup>



### 2. Elimination from Isoindolinium Salts

Wittig's original synthesis of 2-methylisoindole (19) followed this route.<sup>4</sup>



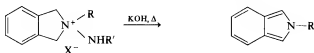
Several examples of this reaction are known, but where a benzyl substituent is present at nitrogen, the reaction is complicated by rearrangements (Sommelet and Stevens rearrangements are observed) to give 1-substituted isoindolines.<sup>5</sup>

<sup>23</sup> G. Cignarella, R. Cerri, G. Grella, and P. Sanna, *Gazz. Chim. Ital.* **106**, 65 (1976).

<sup>24</sup> G. Cignarella and A. Saba, *Ann. Chim. (Rome)* **60**, 765 (1970).

<sup>25</sup> S. A. North, Ph.D. Thesis, London (1981).

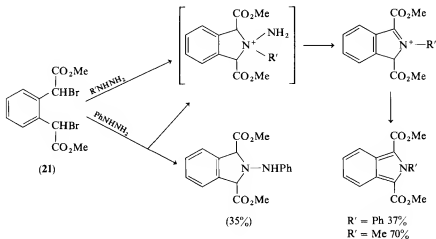
Elimination from 2-aminoisindolinium salts occurs under basic conditions.<sup>26,27</sup> This appears to be a most useful route, particularly with the *N*-*t*-butoxycarbonyl precursors (**20**, R' = CO<sub>2</sub>Bu-*t*). This type of elimina-



(20) R = Me, R' = H, 70% (one stage from *o*-xylene dibromide and methylhydrazine)

R = PhCH<sub>2</sub>, R' = CO<sub>2</sub>Bu-*t*, 46%

tion is also thought to be involved in the reaction of the dibromoester **21** with hydrazine or a substituted hydrazine (Scheme 1). The reactants are kept in an inert solvent, generally under reflux, for several hours. Where phenylhydrazine is used, an alternative pathway, leading to the 2-phenyl-iminoisindoline, is also followed.<sup>28,29</sup>



SCHEME 1

In an approach developed by Kreher and Seubert,<sup>30</sup> the isoindoline *N*-oxides undergo an analogous elimination when treated with an acylating

<sup>26</sup> B. Zeeh and K. H. König, *Synthesis*, 45 (1972).

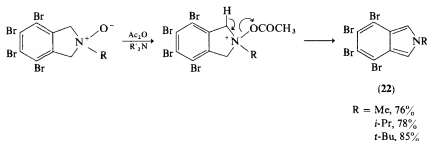
<sup>27</sup> P. S. Anderson, M. E. Christy, C. D. Colton, W. Halczenko, G. S. Ponticello, and K. L. Shepard, *J. Org. Chem.* **44**, 1519 (1979).

<sup>28</sup> G. Cignarella, F. Savelli, R. Cerri, and P. Sanna, *J. Heterocycl. Chem.* **11**, 1049 (1974).

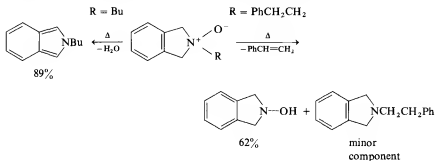
<sup>29</sup> G. Cignarella, F. Savelli, and P. Sanna, *Synthesis*, 252 (1975).

<sup>30</sup> R. Kreher and J. Seubert, *Angew. Chem., Int. Ed. Engl.* **3**, 639 (1964); **5**, 967 (1966).

agent in the presence of base. This route has been employed, for example, in the preparation of 4,5,6,7-tetrabromoisindole derivatives (22).<sup>31</sup>



It may be noted that pyrolysis of isindoline *N*-oxides may also furnish isindoles,<sup>32</sup> although in general this is a less useful preparative route since other reactions (deoxygenation, Cope elimination of the 2-substituent) may intervene,<sup>6</sup> as shown for the 2-( $\beta$ -phenylethyl) derivative in Scheme 2.



SCHEME 2

### 3. Elimination from 2-Substituted Isoindolines

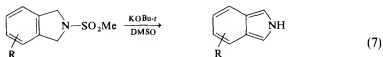
Although early attempts to observe elimination from 2-tosyloisindoline with potassium hydroxide were unsuccessful,<sup>3</sup> subsequent studies using a more hindered but stronger base (e.g., KO*Bu-t*) have shown this type of route to be very useful. Thus, the first demonstration by a trapping experiment of the existence of isindole involved the elimination of benzyl alcohol from 2-benzyloxyisindoline (Eq. 1, Section II,A), and the first isolation of isindole involved formal elimination of methyl hydrogencarbonate (Eq. 2, Section II,A). The elimination of toluenesulfinate has been employed for the synthesis of 1,3-diphenylisindole.<sup>33</sup> More recently, this general ap-

<sup>31</sup> R. Kreher and K. J. Herd, *Z. Naturforsch., Teil B* **29**, 683 (1974).

<sup>32</sup> J. Thesing, W. Schäfer, and D. Melchior, *Justus Liebigs Ann. Chem.* **671**, 119 (1964).

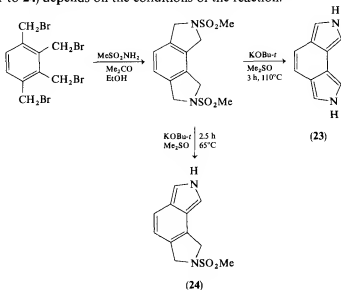
<sup>33</sup> J. C. Emmett and W. Lwowski, *Tetrahedron* **22**, 1011 (1966).

proach has been employed to obtain isoindoles substituted with chlorine,<sup>34</sup> bromine,<sup>35</sup> and methyl<sup>36</sup> functions in the carbocyclic ring as shown in Eq. (7).



R = Cl<sub>4</sub>, Br<sub>4</sub>, Br<sub>2</sub>, Me<sub>2</sub>, Me<sub>2</sub>, etc.

It has also been employed to obtain annelated isoindole systems such as **23** (Scheme 3). In this example the precise course of the elimination (leading to **23** or to **24**) depends on the conditions of the reaction.<sup>37</sup>



SCHEME 3

Several  $\pi$ -annelated isoindole systems, of which **23** is an example, have been described in recent years<sup>38-43</sup> but are outside the scope of this review.

<sup>34</sup> R. Kreher and K. J. Herd, *Tetrahedron Lett.*, 1661 (1976).

<sup>35</sup> R. Kreher and K. J. Herd, *Angew. Chem., Int. Ed. Engl.* **13**, 739 (1974).

<sup>36</sup> R. Kreher and K. J. Herd, *Heterocycles* **11**, 409 (1978).

<sup>37</sup> R. Kreher and K. J. Herd, *Angew. Chem., Int. Ed. Engl.* **17**, 68 (1978).

<sup>38</sup> J. E. Shields and J. Bornstein, *J. Am. Chem. Soc.* **91**, 5192 (1969).

<sup>39</sup> J. Bornstein, D. A. McGowan, A. L. DiSalvo, J. E. Shields, and J. Kopecky, *Chem. Commun.*, 1503 (1971).

<sup>40</sup> R. Kreher and W. Gerhardt, *Tetrahedron Lett.*, 3465 (1977).

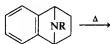
<sup>41</sup> J. Duflos, G. Quéguiner, and P. Pasteur, *J. Chem. Res. (S)*, 39 (1978).

<sup>42</sup> D. E. Remy, F. H. Bissett, and J. Bornstein, *J. Org. Chem.* **43**, 4469 (1978).

<sup>43</sup> J. Bornstein, S. E. Hunt, J. D. Mineck, and D. E. Remy, *J. Org. Chem.* **44**, 805 (1977).

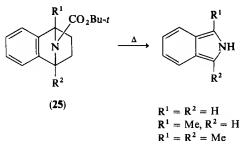


## B. RETRO-CYCLOADDITIONS



These reactions were referred to in Section II,A in connection with the preparation of the parent compound, but they have a much wider application and represent a valuable development in synthesis in this series.

Thus, the pyrolysis of **25** at 600°C/0.5 mm causes a retro-Diels-Alder reaction to ensue with the elimination of ethylene. At the same time the *t*-butoxycarbonyl group thermolyzes to generate carbon dioxide and isobutylene.<sup>16</sup> Hence, this is a useful route to 2-unsubstituted isoindoles.



Related retro-Diels-Alder reactions have been employed to obtain 4,5,6,7-tetrafluoro-2-methylisoindole,<sup>44</sup> 4,5,6,7-tetrafluoroisoindole,<sup>45</sup> and 4,5,6,7-tetrachloro-2-*t*-butylisoindole<sup>46</sup> (Table I).<sup>15-17,44-46a</sup>

Another approach, attributable to Warrener, induces the retro reaction under much milder conditions by ensuring that the dienophile retro fragment is a stabilized (aromatic) species. Again, this route has been applied to the parent compound (Section II,A; Eq. 5), but it has also been employed in the synthesis of 2-ethoxycarbonylisoindole and of 4,5,6,7-tetrafluoro-2-methylisoindole.<sup>17</sup>

However, some failures in this general approach have been noted. The attempted cycloaddition-*retro* reaction of benzyne with the mesoionic 3-methyl-2,4-diphenylthiazolium-5-olate (**26**) is reported to give only very low yields of the expected isoindole.<sup>47</sup>

<sup>44</sup> H. Heaney, S. V. Ley, A. P. Price, and R. P. Sharma, *Tetrahedron Lett.*, 3067 (1972).

<sup>45</sup> J. Bornstein, D. E. Remy, and J. E. Shields, *Tetrahedron Lett.*, 4247 (1974).

<sup>46</sup> M. Ahmed and J. M. Vernon, *Chem. Commun.*, 462 (1976).

<sup>46a</sup> L. K. Kricka and J. M. Vernon, *Adv. Heterocycl. Chem.* **16**, 87 (1974).

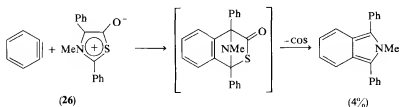
<sup>47</sup> H. Kato, S. Nakazawa, T. Kiyosawa, and K. Hirakawa, *J. C. S. Perkin I*, 672 (1976).

TABLE I  
ISOINDOLES FROM RETRO-CYCLOADDITION REACTIONS

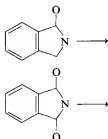
Adduct <sup>a</sup>	Temperature (°C) and pressure	Product	Reference
	600, 0.5 mm		15
<p>(not isolated)            (a) <math>R^1 = R^2 = H</math>            (b) <math>R^1 = CO_2Me</math>, <math>R^2 = H</math>            (c) <math>R^1 = Me</math>, <math>R^2 = F</math></p>	Room temperature (pressure not stated)		17
<p><math>R^1 = CO_2Bu-t</math>            (a) <math>R^2 = R^3 = H</math>            (b) <math>R^2 = Me</math>, <math>R^3 = H</math>            (c) <math>R^2 = R^3 = Me</math></p>	600, 0.5 mm		16
<p>(a) <math>R = H</math>            (b) <math>R = Me</math></p>	(a) 500, 0.5 mm (b) 120, 1 atm (1 week)		45, 44
	> 200 (pressure not stated)		46

$R = Bu-t$

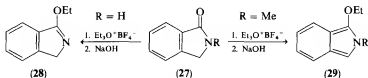
<sup>a</sup> Adducts with the 1,4-epiiminonaphthalene skeleton may be prepared by the Diels-Alder reaction between pyrroles and benzyne.<sup>46a</sup>



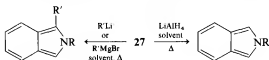
## C. SYNTHESIS FROM PHTHALIMIDINES AND RELATED COMPOUNDS



Although phthalimidine (27, R = H) is formally at the isoindole oxidation level, its chemical properties are those of an amide. The corresponding cyclic imide (28), which is formed from the amide using Meerwein's reagent in the normal way, is an isoindolenine derivative, however. Moreover, when the starting phthalimidine is 2-substituted, the product after basification is a 1-alkoxyisoindole (29).<sup>48,49</sup>

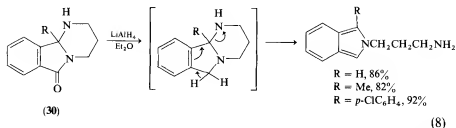


The more general routes from phthalimidines to isoindoles require an addition-dehydration sequence; this is a useful approach to 2-substituted and 1,2-disubstituted systems.<sup>5,27</sup> In a variant of the hydride reduction,

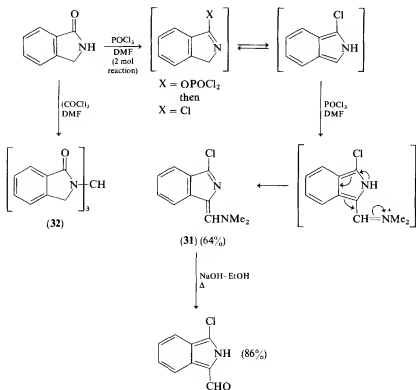


<sup>48</sup> S. Petersen and E. Tietze, *Justus Liebigs Ann. Chem.* **623**, 166 (1959).

<sup>49</sup> R. Kreher and H. Hennige, *Tetrahedron Lett.*, 4695 (1969); 1911 (1973).



the tricyclic system **30** undergoes cleavage (Eq. 8, possible mechanism indicated) to give the 2-substituted isoindole.<sup>50</sup> Certain other fused phthalimidine systems have been found to generate isoindoles on hydride reduction.<sup>50,51</sup>



SCHEME 4

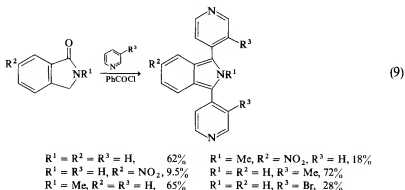
<sup>50</sup> P. Aeberli and W. J. Houlihan, *J. Org. Chem.* **34**, 1720 (1969); see also A. Nakamura and S. Kamiya, *Chem. Pharm. Bull.* **22**, 2142 (1974).

<sup>51</sup> M. E. Winn and H. E. Zaugg, *J. Org. Chem.* **34**, 249 (1969).

von Dobeneck and his colleagues have reported some interesting reactions of phthalimidines. Treatment of phthalimidine with two molar equivalents of the Vilsmeier reagent, followed by basic hydrolysis, gives the 1-formyl-3-haloisoindole.<sup>52</sup> The reaction has been carried out for bromine and chlorine as the halogen substituent, and the products appear to have potential as synthetic intermediates in the isoindole series. The reaction proceeds via the isoindolenine derivative **31** which may arise as shown in Scheme 4.

Reaction of phthalimidine with an equimolar ratio of oxalyl chloride-dimethylformamide generates tris(1-oxoisoindolin-2-yl)methane (**32**).<sup>52</sup>

In a subsequent publication, the same workers reported the synthesis of a number of 1,3-di(4-pyridyl)isoindoles by the reaction of a phthalimidine with an excess of the pyridine in the presence of benzoyl chloride (Eq. 9).



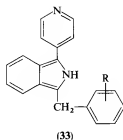
Besides the examples given in Eq. (9), the reaction has been carried out with other pyridines and with quinolines and isoquinolines.<sup>53</sup> Examples of this reaction with various 3-benzylphthalimidine derivatives have also been reported to give remarkably high yields of isoindoles formulated as shown in structure **33**.<sup>53</sup> These reactions deserve further study.

Conditions for the formation of isoindoles by the reduction of phthalimides have proved difficult to establish. Reduction of phthalimide itself with lithium aluminum hydride gives isoindoline. However, Garmaise and Ryan<sup>54</sup> have shown that *N*-benzylphthalimide can be reduced with a modified hydride reductant [sodium bis(2-methoxyethoxy)aluminum hydride] to give 2-benzylisoindole in moderate yield under mild conditions.

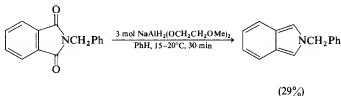
<sup>52</sup> H. von Dobeneck, H. Reinhard, H. Deubel, and D. Wolkenstein, *Chem. Ber.* **102**, 1357 (1969).

<sup>53</sup> H. von Dobeneck, D. Wolkenstein, H. Deubel, and H. Reinhard, *Chem. Ber.* **102**, 3500 (1969).

<sup>54</sup> D. L. Garmaise and A. Ryan, *J. Heterocycl. Chem.* **7**, 413 (1970).

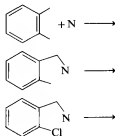


R = H,	82% (as B · HCl)
R = 2-Cl,	70%
R = 3-Cl,	86%
R = 4-Cl,	88%
R = 2-OCOPh,	75%



The general utility of this reaction remains in doubt, however. Reduction of *N*-(pent-4-enyl)phthalimide gives a mixture containing about equal amounts of the isoindole and isoindoline, with a smaller amount of the phthalimidine.<sup>55</sup>

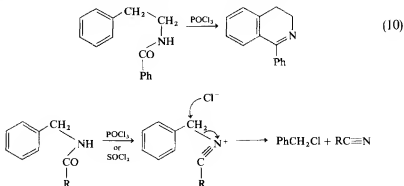
#### D. SYNTHESSES FROM ORTHO-DISUBSTITUTED BENZENES



In this approach the heterocycle is built on to an existing benzenoid ring. Of course, some of the reactants—isoindolines, phthalimidines, and phthalimides—considered in some of the previous sections may have had *o*-disubstituted benzenes as precursors. Here we consider reactions that lead directly to isoindoles.

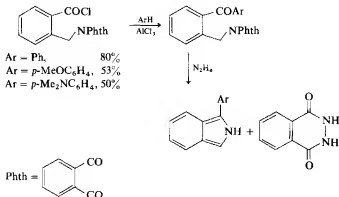
<sup>55</sup> E. Ciganek, *J. Org. Chem.* **45**, 1512 (1980).

The Bischler–Napieralski reaction for the synthesis of 3,4-dihydroisoquinolines (Eq. 10) cannot be extended to prepare isoindoles,<sup>2</sup> presumably because an alternative pathway (von Braun reaction) is favored.<sup>2,5</sup>



### 1. Routes via 2-Aminomethylphenyl Ketones and Aldehydes and Equivalent Systems

Perhaps the most useful route here is that described by Veber and Lwowski<sup>12</sup> (Scheme 5) and reviewed earlier.<sup>5</sup>

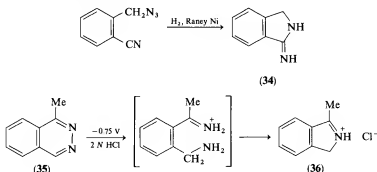


SCHEME 5

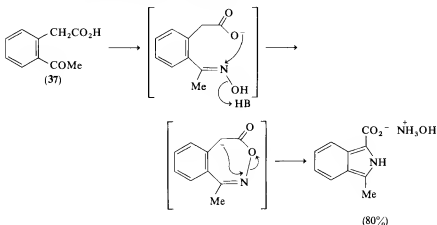
Various reduction processes to generate the aminomethyl function *in situ* have been reported. Thus, hydrogenation of *o*-cyanobenzophenone over Raney nickel gives 1-phenylisoindole<sup>56</sup>; similar reduction of *o*-azidomethyl-

<sup>56</sup> R. Kreher and J. Seubert, *Tetrahedron Lett.*, 3015 (1966).

benzonitrile furnishes **34** (56%).<sup>57</sup> The electrochemical reduction of 1-methylphthalazine (**35**) under acidic conditions furnishes 1-methylisindole as the hydrochloride (**36**).<sup>13</sup>



A related cyclization process has been reported to give the isindole carboxylic acid derivative as its hydroxylammonium salt when the keto acid **37** is refluxed in aqueous ethanol with two molar equivalents of hydroxylamine.<sup>58</sup> A plausible pathway is indicated.



## 2. Routes via ortho-Dicarbonyl Derivatives

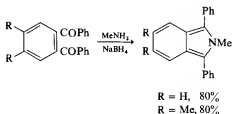
1,3-Diphenylisindole can be conveniently prepared from *o*-dibenzoyl benzene, for example, by treatment with ammonium formate (Leuckart reaction).<sup>5,33</sup> The same type of reaction is observed when the aryl diketone

<sup>57</sup> R. Kreher and H. Hennige, *Z. Naturforsch., Teil B* **28**, 801 (1973).

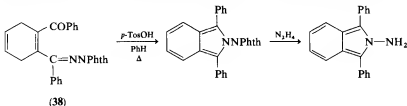
<sup>58</sup> H. Kotake, H. Kinoshita, and S. Miyashita, *Chem. Lett.* **6**, 445 (1972).



is treated with methylamine and sodium borohydride.<sup>59</sup> Other related reac-

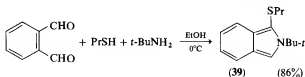


tions have been studied.<sup>60,61</sup> Thus, cyclization of the phthaloylhydrazone **38**, followed by hydrazinolysis, gives 2-amino-1,3-diphenylisoindole.<sup>60</sup>



Phthalaldehyde has also been employed as a precursor. 2-Arylisoindoles are formed when phthalaldehyde is reacted with primary aromatic amines in the presence of potassium tetracarbonylhydride. In some examples, reduction to the isoindoline level also occurs, and this is the main pathway when aliphatic amines are employed.<sup>62</sup> The reactions of phthalaldehyde with ammonia and with amines in the *absence* of a reducing agent give complex mixtures. With ammonia, the major products are phthalimidine and 3-(2-cyanophenyl)isoquinoline.<sup>63</sup>

Simons and Johnson<sup>64,65</sup> prepared the first thioether derivative (**39**) of an isoindole by the reaction of phthalaldehyde and an amine in the presence



<sup>59</sup> M. J. Haddadin and N. C. Chelhot, *Tetrahedron Lett.*, 5185 (1973).

<sup>60</sup> D. W. Jones, *J. C. S. Perkin I*, 2728 (1972).

<sup>61</sup> D. Olliero and G. Solladie, *Synthesis*, 246 (1975).

<sup>62</sup> Y. Watanabe, S. C. Shim, H. Uchida, T. Mitsudo, and Y. Takegami, *Tetrahedron* **35**, 1433 (1979).

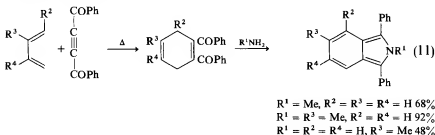
<sup>63</sup> T. DoMinh, A. L. Johnson, J. E. Jones, and P. P. Senise, *J. Org. Chem.* **42**, 4217 (1977).

<sup>64</sup> S. S. Simons and D. F. Johnson, *J. C. S. Chem. Commun.*, 374 (1977).

<sup>65</sup> S. S. Simons and D. F. Johnson, *J. Org. Chem.* **43**, 2886 (1978).

of an alkylthiol. Several analogs of **39** have been prepared. These compounds are strongly fluorescent, and this property has been used as the basis of a sensitive detection method for amines, especially of amino acids, peptides, and proteins.<sup>66,67</sup> Indeed, it was the observation<sup>66</sup> of this fluorescence (with phthalaldehyde, 2-mercaptoethanol, and primary amines) that led to this synthesis.

The syntheses described above in which a benzenoid *ortho*-dicarbonyl derivative reacts with an amine require two reducing equivalents to proceed smoothly to the isoindole oxidation level. The synthesis described by White and Mann<sup>5,68</sup> accommodates this feature by employing a 1,4-dihydrobenzene derivative (Eq. 11).



### 3. Routes via *ortho*-Dicyano Derivatives

Phthalonitrile serves as a precursor for a variety of isoindolenine derivatives. Thus, heating with ammonia in methanol gives 1,3-diiminoisoindoline (**40**),<sup>69,70</sup> while treatment with sodium methoxide and then with methanol is reported to give compounds **41** and **42**, respectively (Scheme 6).<sup>71</sup> Irradiation of 1,2,4,5-tetracyanobenzene in methanol and benzene, or refluxing the same solution, gives the dicyano derivative of **42**.<sup>72</sup> Phthalonitrile reacts with phenols (alone, or acid-catalyzed) to give, depending on the conditions, the products **43** and **44** of *C*-substitution (Scheme 6).<sup>73</sup>

<sup>66</sup> J. R. Benson and P. E. Hare, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 619 (1975).

<sup>67</sup> S. S. Simons and D. F. Johnson, *J. Am. Chem. Soc.*, **98**, 7098 (1976); *Anal. Biochem.*, **90**, 705 (1978).

<sup>68</sup> J. D. White, M. E. Mann, H. D. Kirshenbaum, and A. Mitra, *J. Org. Chem.*, **36**, 1048 (1971).

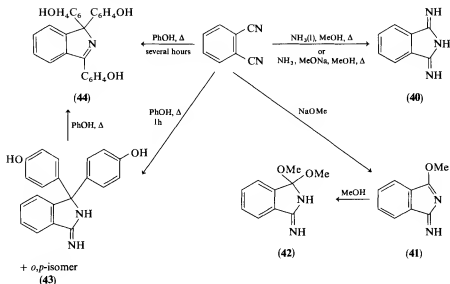
<sup>69</sup> J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 5000 (1952).

<sup>70</sup> M. K. Lowery, A. J. Starshak, J. N. Esposito, P. C. Krueger, and M. E. Kennedy, *Inorg. Chem.*, **4**, 128 (1965).

<sup>71</sup> E. V. Pankratova, G. N. Rodionova, B. E. Zaitsev, and V. Titkov, *Khim. Geterotsikl. Soedin.*, 63 (1977) [*CA* **86**, 155448 (1977)].

<sup>72</sup> S. Yamada, Y. Kimura, and M. Ohashi, *J. C. S. Chem. Commun.*, 667 (1977).

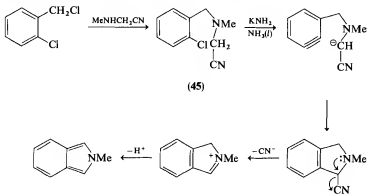
<sup>73</sup> R. K. Bartlett, L. V. Renny, and K. K. Chan, *J. Chem. Soc. C*, 129 (1969).



SCHEME 6

#### 4. Aryne Cyclization

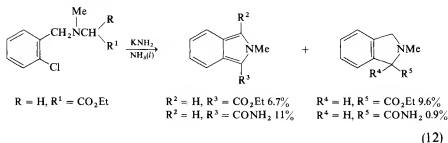
A number of examples of the aryne cyclization route have appeared. Treatment of the appropriately substituted halobenzene (45) with potassium amide in liquid ammonia affords 2-methylisindole in 89% yield.<sup>74</sup> A rationalization of the reaction is shown in Scheme 7. This route has been



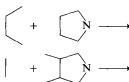
SCHEME 7

<sup>74</sup> B. Jaques and R. G. Wallace, *Tetrahedron* 33, 581 (1977).

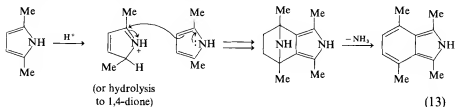
explored to obtain a number of 1-substituted 2-alkylisoindoles. Yields are variable and isoindolines are sometimes observed as by-products (Eq. 12).<sup>75</sup>



### E. ROUTES FROM PYRROLES



The condensation of 2,5-disubstituted pyrroles or 1,2,5-trisubstituted pyrroles with 1,4-diones under acidic conditions generates the isoindole system. This is a convenient route (i.e., with 2,5-disubstituted pyrroles) to *N*-unsubstituted (and therefore potentially tautomeric) compounds.<sup>5,76-78</sup> Certain isoindoles can be obtained directly from the 1,4-dione and ammonia or primary amine under acidic conditions<sup>77</sup> or by the self-condensation of 2,5-disubstituted pyrroles under acidic conditions<sup>78</sup> (Scheme 8). The pyrrole self-condensation may be rationalized as shown in Eq. (13); the other reactions are mechanistically analogous.

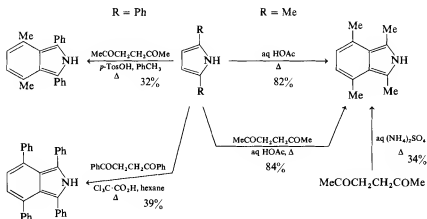


<sup>75</sup> I. Ahmed, G. W. H. Cheeseman, B. Jaques, and R. G. Wallace, *Tetrahedron* **33**, 2255 (1977); cf. R. Jaunin, Ger. Offen. 2733886 (1978) [*CA* **88**, 152424 (1978)].

<sup>76</sup> F. H. Norton, U.S. Patent 3,007,939 (1959) [*CA* **56**, 7281 (1962)].

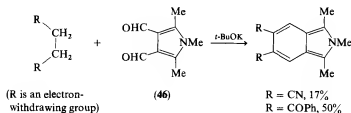
<sup>77</sup> H. Fletcher, *Tetrahedron* **22**, 2481 (1966).

<sup>78</sup> C. O. Bender and R. Bonnett, *J. Chem. Soc. C*, 3036 (1968).



SCHEME 8

Alternatively, it is possible to use a 3,4-diformylpyrrole as the precursor.<sup>79</sup> Thus, the condensation of succinonitrile or of 1,2-dibenzoylthane with the 3,4-diformylpyrrole derivative (**46**) under basic conditions gives the corresponding isoindoles in yields of 17 and 50%, respectively.



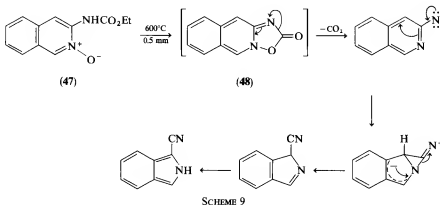
## F. REARRANGEMENTS AND OTHER REACTIONS

Pyrolysis of 3-ethoxycarbonylaminoisoquinoline 2-oxide (**47**) gives 1-cyanoisoindole quantitatively.<sup>80</sup> The reaction is rationalized in terms of an intermediate oxadiazolone (**48**) which loses carbon dioxide to give a nitrene which is postulated to cyclize as shown (Scheme 9).

1-Cyanoisoindole has also been obtained as a ring-contraction product in the reaction of 3-amino-4-bromoisoquinoline with potassium amide in

<sup>79</sup> R. Kreher and G. Vogt, *Angew. Chem. Int. Ed. Engl.* **9**, 955 (1970).

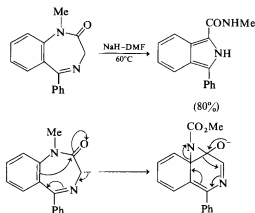
<sup>80</sup> R. F. C. Brown and R. J. Smith, *Aust. J. Chem.* **25**, 607 (1972).



SCHEME 9

liquid ammonia. Rather low yields of the isoindole were obtained, and 3-aminoisoquinoline was also produced.<sup>81</sup>

Several examples<sup>82</sup> have been reported of the rearrangement of benzo-diazepins to isoindole-1-carboxylic acid derivatives, a reaction originally discovered and rationalized by Fryer and his colleagues (Scheme 10).<sup>83</sup>



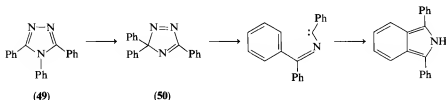
SCHEME 10

<sup>81</sup> G. M. Sanders, M. van Dijk, and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas* **93**, 298 (1974).

<sup>82</sup> R. Jaunin, Ger. Offen. 2,553,595 (1976) [*CA* **86**, 29623 (1977)]; Ger. Offen. 2,723,186 (1977) [*CA* **88**, 62294 (1978)].

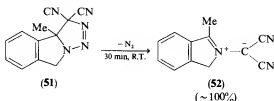
<sup>83</sup> R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Am. Chem. Soc.* **88**, 3173 (1966); R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc. C*, 366 (1967).

Vacuum pyrolysis of the 1,3,5- and 3,4,5-triphenyl derivatives of 1,2,4-triazole gives 1,3-diphenylisoindole in 21% yield. The proposed mechanism, shown for the 3,4,5-triphenyl derivative (**49**) involves rearrangement into



the nonaromatic heterocycle **50**, which loses dinitrogen, generating a carbene, which cyclizes.<sup>18</sup> 1-Phenylisoindole and isoindole (Section II.A) have been approached in the same way.<sup>18</sup>

Elimination of nitrogen is also observed during the thermal decomposition of the triazoline **51**. This reaction leads to the azomethine ylide system **52**, the structure of which has been determined by X-ray crystallography.<sup>84,85</sup>



Various routes to 1,1,3-trisubstituted 1*H*-isoindoles have been reviewed.<sup>5</sup> Thus, the triphenyl derivative **53** is available from the reaction of benzophenone imine with diphenyldichloromethane or by the Friedel-Crafts reactions between benzene and 1,1,3-trichloro-1*H*-isoindole. Recently, another route, which involves heating the cyclotriphosphatriazene **54** with benzophenone, has been described.<sup>86</sup> The nitron derivative **55** of the isoindolenine **53** may be obtained by treating the isoindolenine with *m*-chloroperbenzoic acid. This nitron has also been obtained by the isomerization of the oxaziran **56** in the presence of a Lewis acid (Scheme 11).<sup>87</sup>

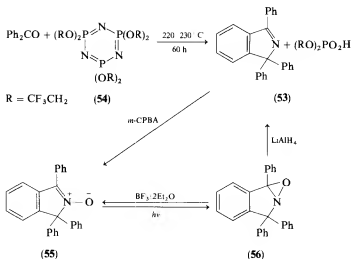
In summary, although some of the procedures have limited applicability, there is now considerable variety in the synthetic routes available to the isoind-

<sup>84</sup> R. Rømming and P. Kolsaker, *Acta Chem. Scand.* **B32**, 679 (1978).

<sup>85</sup> P. Kolsaker, P. O. Ellingsen, and G. Wøien, *Acta Chem. Scand.* **B32**, 683 (1978).

<sup>86</sup> R. A. Shaw and E. T. Mukmenev, *Dokl. Akad. Nauk SSSR* **208**, 379 (1973) [*CA* **79**, 126222 (1973)].

<sup>87</sup> B. Singh, *J. Am. Chem. Soc.* **90**, 3893 (1968).



SCHEME 11

dole system. Shepard and his colleagues,<sup>27</sup> to prepare an extensive range of substituted isoindoles, selected the elimination from 2-aminoisoindolinium salts (Section III,A,2) and routes starting from phthalimidines (Section III,C).

## IV. Theoretical and Physical Aspects

### A. THEORETICAL ASPECTS

Isoindole is a  $\pi$ -excessive 10- $\pi$ -electron heteroaromatic system. In valence bond terms the delocalized system can be described in a conventional way by the canonical forms **57**–**61**, where **57** is of major importance. The situation here is rather analogous to that with pyrrole, but the dipolar structures

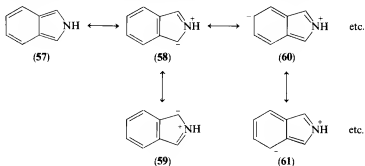




TABLE II  
 CALCULATED GROUND-STATE  $\pi$ -ELECTRON DENSITIES FOR ISOINDOLE

Position	Ref. 92 (1961)	Ref. 90 (1970)	Ref. 93 (1972)	Ref. 89 (1976)	Ref. 94 <sup>a</sup> (1976)
1 (3)	1.112	1.059	1.155	1.126	1.108
2 (N)	1.502	1.807	1.538	1.552	1.626
4 (7)	1.016	0.998	1.011	1.002	1.010
5 (6)	1.041	1.009	1.018	1.024	1.020
3a (7a)	1.081	1.031	1.047	1.073	1.049

<sup>a</sup> Refers to 2-methylisindole.

**58** and **59** retaining the benzenoid ring are expected to be relatively more important than extended dipolar structures such as **60** and **61**.

Because of its late arrival on the chemical scene, isindole became something of a favorite with the theoreticians. The earliest calculations appear to be those of Dewar (1946).<sup>88</sup> There is no experimental value for the resonance energy of isindole. Palmer and Kennedy<sup>89</sup> quote calculated values of 252 kJ mol<sup>-1</sup> for isindole, 308 kJ mol<sup>-1</sup> for indole, and 212 kJ mol<sup>-1</sup> for benzene. Other calculated values have appeared.<sup>5,90-92</sup> Although there is considerable variation of approach and numerical result, there is general agreement, at least in recent years, that the resonance energy of isindole is less than those of indole and naphthalene and greater than those of pyrrole and benzene. The resonance energy of isindoline is thought to be less than that of isindole by about 30 kJ mol<sup>-1</sup>.<sup>12</sup>

The dipole moment of isindole has not been measured but has been predicted to be 2.94 debye.<sup>89</sup>

Molecular orbital (MO) calculations have generated  $\pi$ -electron density values, some of which are presented in Table II.<sup>89,90,92-94</sup> There is agreement among recent calculations concerning two features—first, that the ground-state  $\pi$ -electron density is highest at C-1 (C-3); second, that in the benzenoid ring  $\pi$ -electron density is higher at C-5 (C-6) than at C-4 (C-7). Insofar as  $\pi$ -electron densities tend to be useful reactivity parameters in  $\pi$ -excessive systems, this order accords with the ease of electrophilic substitution at C-1 (C-3) (Section V,D).

<sup>88</sup> M. J. S. Dewar, *Trans. Faraday Soc.* **42**, 764 (1946).

<sup>89</sup> M. H. Palmer and S. M. F. Kennedy, *J. C. S. Perkin II*, 81 (1976).

<sup>90</sup> J. S. Dewar, A. J. Harget, N. Trinajstić, and S. D. Worley, *Tetrahedron* **26**, 4505 (1970).

<sup>91</sup> B. A. Hess, L. J. Schaad, and C. W. Holyoke, *Tetrahedron* **28**, 3657 (1972).

<sup>92</sup> O. E. Polansky and G. Derflinger, *Monatsh. Chem.* **92**, 1114 (1961).

<sup>93</sup> L. Klasinc, E. Pop, N. Trinajstić, and J. V. Knop, *Tetrahedron* **28**, 3465 (1972).

<sup>94</sup> W. Rettig and J. Wirz, *Helv. Chim. Acta* **59**, 1054 (1976).

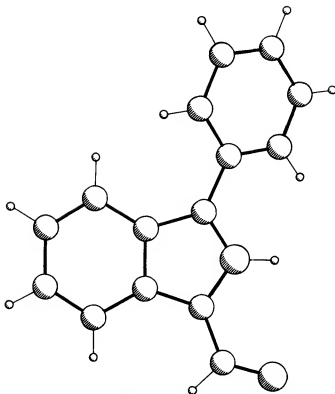
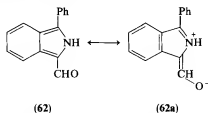


FIG. 4. The molecular structure of 1-formyl-3-phenylisindole.<sup>95</sup>

The X-ray structure analysis of 1-formyl-3-phenylisindole (**62**) has been carried out.<sup>95</sup> The molecular structure is shown in Fig. 4 and bond lengths and bond angles are given in Fig. 5.



That the N2—C3 bond (1.348 Å) is shorter than the C1—N2 bond (1.376 Å) is attributed to the contributions of the polarized canonical

<sup>95</sup> S. A. North and J. Trotter, unpublished results.

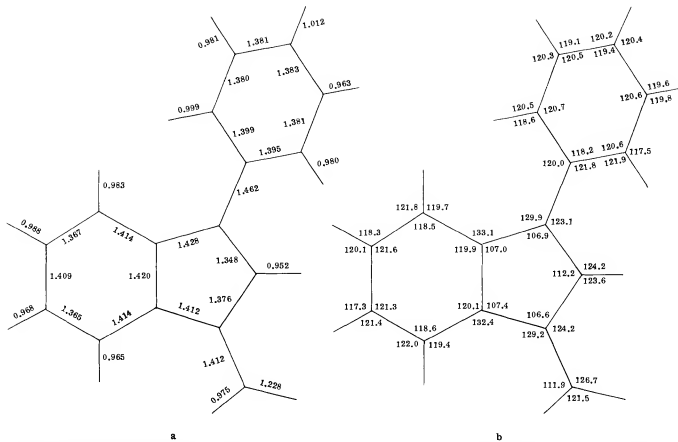


FIG. 5. Bond distances and angles in 1-formyl-3-phenylisindole.<sup>95</sup> (a) esd's 0.002 Å; 0.015–0.018 Å for bonds to hydrogen. (b) esd's 0.1°; 0.9–1.1° for bond angles involving hydrogen.

TABLE III  
 BOND LENGTHS FOR ISOINDOLES AND RELATED SYSTEMS

System	Bond lengths (Å)						Reference
Isoindoles	1-2 (2-3)	1-7a (3-3a)	4-5 (6-7)	3a-4 (7-7a)	5-6	3a-7a	
1-Formyl-3-phenyl- isoindole <sup>a</sup>	1.376 (1.348)	1.412 (1.428)	1.367 (1.365)	1.414 (1.414)	1.409	1.420	95
2-Methylisoindole <sup>b</sup>			1.37		1.43		94
Isoindole <sup>c</sup>	1.384	1.370	1.357	1.456	1.448	1.440	90
Isoindolenine-like system							
<b>52</b> (X = Y = CN) <sup>a</sup>	1.320 (1.482)	1.458 (1.489)	1.387 (1.395)	1.384	1.374	1.387	84
Naphthalene			1-2	1-8a	2-3	4a-8a	
<i>a</i>			1.378	1.424	1.411	1.421	96
<i>b</i>			1.37		1.41		94
Cyclohexa-1,3-diene							
<i>d</i>			1.339		1.467		97

<sup>a</sup> Values from X-ray structure analysis.<sup>b</sup> Values from coupling constants.<sup>c</sup> Values from MO calculations.<sup>d</sup> Values from electron diffraction.

structure **62a**. The presence of the formyl group thus polarizes the structure (cf. pyrrole chemistry) and complicates comparisons with bond distances calculated for the parent compound. However, bond lengths for various isoindoles<sup>84,90,94-97</sup> have also been derived from NMR coupling constants,<sup>20,68,94,98-100</sup> and some comparisons are made in Table III. Clearly, the six-membered ring is a delocalized system (cf. bond lengths for cyclohexa-1,3-diene, Table III), but within the delocalized system there remains marked bond alternation, which is also observed in naphthalene and which had been predicted for isoindole. In contrast, the azomethine ylide system **52**, which is an isoindolenine derivative (albeit not a typical one), shows little or no alternation of bond lengths in the six-membered ring.

<sup>96</sup> V. I. Ponomarev, O. S. Filipenko, and L. O. Atovmyan, *Sov. Phys.—Crystallogr. (Engl. Transl.)* **21**, 215 (1976) [*CA* **84**, 187972 (1976)].

<sup>97</sup> G. Dallinga and L. H. Toneman, *J. Mol. Struct.* **1**, 11 (1968).

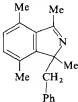

<sup>98</sup> E. Chacko, J. Bornstein, and D. J. Sardella, *J. Am. Chem. Soc.* **99**, 8248 (1977).

<sup>99</sup> B. A. Hess and L. J. Schaad, *Tetrahedron Lett.*, 535 (1977).

<sup>100</sup> M. A. Cooper and S. L. Manatt, *J. Am. Chem. Soc.* **91**, 6325 (1969).

It has been suggested (Ref. 98, but contrast Ref. 99) that isoindole can be regarded as made up of pyrrole and butadiene  $\pi$ -systems which are "contiguous but virtually noninteracting." This view does not appear to receive adequate support from calculation or experiment on the isoindole structures referred to above and is at variance with the results of cycloaddition reactions which for the ground state typically occur across the 1,3-positions and not across the 4,7-positions (Section V,E).

TABLE IV  
ELECTRONIC SPECTRA OF SOME ISOINDOLES AND ISOINDOLENINES

Compound	Solvent	$\lambda_{\max}$ (nm) (log $\epsilon_{\max}$ )	Reference
<b>A. Isoindoles</b>			
Isoindole	Hexane	230, 263.5, 268.5, 275, 286.5, 294 (i), 300, 306.5, 312.5, 320, 326.5, 335.	6
1-Phenylisoindole	EtOH	272 (3.86), 282 (3.92), 314 (i, 3.87), 325 (3.99), 357 (4.10)	33
2- <i>p</i> -Tolylisoindole	MeOH	242 (4.50), 288 (3.94), 298 (3.94), 337 (3.62)	30
1,3,4,7-Tetramethylisoindole	EtOH	249, 289, 298, 347	78
1-Cyanoisoindole	EtOH	222 (4.52), 242 (4.08), 249 (4.05), 256 (4.04), 320 (3.98), 327 (4.04), 341 (3.89)	80
1-Methoxycarbonylisoindole	EtOH	228 (4.32), 256 (4.17), 262 (4.23), 336 (4.22), 350 (4.19)	23
1,3-Dimethoxycarbonylisoindole	MeOH	223 (4.25), 248 (4.58), 345 (4.35), 362 (4.37)	24
<b>B. Isoindolenines</b>			
	EtOH	252 (3.82), 291 (3.23), 301.5 (3.18)	78
	Dioxane	$\sim 220$ (i, 4.45), $\sim 250$ (i, 4.20), $\sim 265$ (i, 3.90) (values read from curve)	101

## B. SPECTROSCOPIC RESULTS

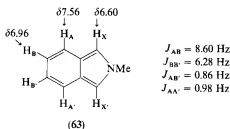
1. *Electronic Spectra*

The absorption spectra of isoindoles show a series of strong bands in the near ultraviolet region extending in cases of further conjugation almost into the visible region. The band at longest wavelength ( $\geq 310$  nm) is generally well separated from the rest of the spectrum and often possesses vibrational fine structure (e.g., Fig. 3); isoindolenines do not possess this absorption. The vibrational fine structure for 2-methylisoindole has been analyzed in terms of two dominant vibrational progressions of  $1400 \pm 50$  and  $550 \pm 50$   $\text{cm}^{-1}$ , which become more distinct when the spectrum is observed in a hydrocarbon glass at 77K.<sup>94</sup> Some typical spectra are given in Table IV<sup>6,23,24,30,33,78,80,101</sup>; in some cases, because of the instability of the substrate, molar extinctions are not available. Tables of spectra have also been collected elsewhere.<sup>5,23,24,65,68</sup>

Some measure of agreement exists between the observed parameters (transition energy, oscillator strength, and polarization) of the electronic spectra and values derived from molecular orbital calculations.<sup>93,94</sup>

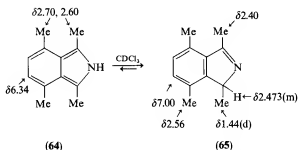
2. *Nuclear Magnetic Resonance Spectra*

The proton magnetic resonance spectrum of isoindole (Section II,B, Fig. 2) displays chemical shifts which are below the normal range for olefinic protons and provides experimental evidence for the aromaticity of the system on the induced ring current criterion.<sup>6</sup> The spectrum of 2-methylisoindole in  $\text{C}_6\text{D}_6$  (and in  $\text{CDCl}_3$ )<sup>89</sup> has been analyzed in detail, and the resulting parameters are given at structure 63.<sup>94</sup> The chemical shifts for the six-membered ring protons (H-4,  $\delta 7.56$ ; H-5,  $\delta 6.96$ ) are well downfield of the corresponding

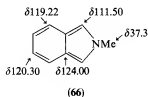


<sup>101</sup> W. Theilacker, H. J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Justus Liebig's Ann. Chem.* **673**, 96 (1964).

protons in cyclohexa-1,3-diene (H-1,  $\delta$ 5.68; H-2,  $\delta$ 5.83).<sup>100</sup> The isoindole–isoindolenine equilibrium (Section V,B) is conveniently examined by NMR spectroscopy.<sup>12,20,102</sup> The chemical shifts for one example, 1,3,4,7-tetramethylisoindole, are shown in structures **64** and **65**.<sup>78</sup> Tables of NMR data have been published.<sup>65,68</sup>



The <sup>13</sup>C-NMR spectrum of 2-methylisoindole has been reported;<sup>89</sup> the chemical shift assignments are shown in structure **66**.

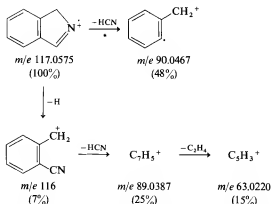


### 3. Mass Spectra

Aromatic systems frequently show prominent molecular ions in electron-impact mass spectra, and isoindoles are no exception. In isoindole itself, the molecular ion is the base peak. The cleavage of the five-membered ring with loss of hydrogen cyanide also generates a prominent ion. Further cleavages, some of which are supported by accurately measured ions,<sup>22</sup> are shown in Scheme 12.

The mass spectrum of 1,3,4,7-tetramethylisoindole also shows the molecular ion as the base peak. For 2-*n*-butylisoindole, while the molecular ion is strong (70%), the base peak at *m/e* 131 appears to arise by loss of propene from the molecular ion.<sup>6,22</sup>

<sup>102</sup> C. O. Bender, R. Bonnett, and R. G. Smith, *J. Chem. Soc. C*, 1251 (1970).



SCHEME 12 Main features of the electron-impact mass spectrum of isindole, with structural rationalizations.<sup>22</sup>

#### 4. Other Spectroscopic Observations

The fluorescence and phosphorescence spectra of 2-methylisindole have been recorded.<sup>94</sup> The fluorescence, the maximum of which occurs at about 363 nm, is structured and bears a classical mirror-image relationship to the low-energy absorption bands. The fluorescence has the following characteristics:  $\phi_f = 0.88 \pm 0.15$ ,  $\tau_f = 12$  nsec. The energy of the first excited singlet (taken as the mean of the energies of the 0–0 bands in absorption and emission) is  $350 \text{ kJ mol}^{-1}$ . No excimer fluorescence is observed for 2-methylisindole in hexane, even up to concentrations of  $10^{-2} \text{ M}$ .

Phosphorescence of 2-methylisindole is weak. It can be observed in an EPA glass at 77K and occurs at 526 nm ( $\phi_p = 0.08 \pm 0.05$ ,  $\tau_p = 0.4 \text{ sec}$ ). Benzophenone is an efficient triplet sensitizer in this system and hence enhances this emission. Triplet–triplet absorption spectra have been measured in flash-photolysis studies; the use of sensitizers and quenchers confirms the triplet energy as  $227 \text{ kJ mol}^{-1}$ .<sup>94</sup>

The photoelectron spectrum of 2-methylisindole has been recorded and the derived ionization potentials discussed in relation to calculated values on this and other heteroaromatic systems.<sup>89,90,94</sup>

The infrared spectra of isindoles are unexceptional; the NH bond, when present, shows a strong stretching vibration at  $3400\text{--}3500 \text{ cm}^{-1}$ . Generally there are one or two bands in the  $1600 \text{ cm}^{-1}$  region, and, in appropriate cases, aromatic C—H out-of-plane deformations occur in the  $800 \text{ cm}^{-1}$  region (e.g., 1,3,4,7-tetramethylisindole<sup>78</sup>  $1610, 1570, 810 \text{ cm}^{-1}$ ; 2-*n*-butylisindole<sup>6</sup>  $1660, 1550, 758 \text{ cm}^{-1}$ ).

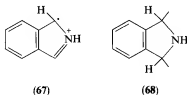


## V. Reactions of Isoindoles

### A. STABILITY

The kinetic instability of isoindoles dominates the chemistry of the simple systems and is principally to be ascribed to autoxidation and self-condensation reactions. The self-condensation reactions appear to be more important when both isoindole and isoindolenine tautomers can coexist (Eq. 6); hence, in general, *N*-substituted isoindoles are more stable than *N*-unsubstituted compounds. Although the autoxidation reactions have been worked out in several cases (Section V,G), the self-condensations are less well understood (but see Section V,F). Isoindole and *C*-alkylisoindoles become dark when kept at room temperature.<sup>6,78</sup> *C*-Arylisoindoles are somewhat easier to handle, but 2-amino-1,3-diphenylisoindole decomposes rapidly on exposure to light and air.<sup>60</sup> Operationally, unless strongly electron-withdrawing substituents are present at carbon, isoindoles must be kept in the freezer under nitrogen.

In our view, the explanation for this high reactivity is not to be ascribed to a lack of aromaticity: these compounds have resonance energies in excess of that of benzene (Section IV,A). Rather, the reactivity is thought to be due to the ease with which this  $\pi$ -excessive heteroaromatic system can undergo one-electron oxidation or 1,3-addition to generate another aromatic (benzenoid) system, as shown at structures **67** and **68**, respectively. In terms of more familiar systems, the reactivity of the 1,3-positions of isoindole may be thought of as a compounding of the reactivity at the  $\alpha$ -positions of pyrrole with that at the meso positions of anthracene.



In accordance with this view, electron-withdrawing substituents at carbon considerably stabilize the system. Thus, 1,3-di(4-pyridyl)isoindole appears to be relatively inert,<sup>53</sup> and 4,5,6,7-tetrafluoro-2-methylisoindole has survived unchanged for 6 months at room temperature in air.<sup>44</sup> 4,5,6,7-Tetrafluoroisoindole is less inert, gradually darkening at room temperature,<sup>45</sup> illustrating the relative reactivities of the *N*-substituted and *N*-unsubstituted systems referred to above. Steric factors also play a part: 1,3,4,7-tetramethylisoindole, in spite of possessing four electron-donor groups, is more easily manipulated than is the parent compound.

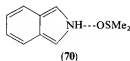
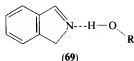
TABLE V  
 ISOINDOLE TAUTOMERISM: EFFECT OF SOLVENT

Solvent	Isoindole tautomer (%)			
	1-Phenyl	1- <i>p</i> -Methoxyphenyl	1- <i>p</i> -Dimethyl-aminophenyl	1,3,4,7-Tetramethyl
CCl <sub>4</sub>	96	—	—	20
C <sub>6</sub> D <sub>6</sub>	—	84	80	24
CDCl <sub>3</sub>	91	69	50	10
EtOH	—	—	—	15
Et <sub>2</sub> O	—	99	—	43
C <sub>5</sub> D <sub>5</sub> N	—	—	~100	84
(CD <sub>3</sub> ) <sub>2</sub> SO	—	—	—	95
Reference	12	12	12	101

## B. TAUTOMERISM

Tautomerism involving the isoindole (2*H*-isoindole) (**1**) and isoindolenine (1*H*-isoindole) (**2**) structures is possible for *N*-unsubstituted isoindoles. The tautomeric ratio is subject both to solvent and substituent effects and has been studied using NMR spectroscopy and electronic spectroscopy. In one case (1-aminocarbonyl-2-methyl-3-phenylisoindole), both tautomers have been isolated.<sup>83</sup>

The effect of solvent variation is illustrated in Table V. The results suggest that, with respect to the value in neutral solvents, hydroxylic solvents tend to favor the isoindolenine form (hydrogen-bonded as in **69**), while solvents which act as an electron source for hydrogen bonding tend to stabilize the isoindole tautomer (as in **70**).



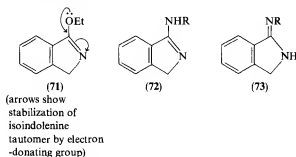
The effect of substituents is profound. Isoindole itself appears to be essentially present as the isoindole tautomer. As Table VI shows, a 1-methyl substituent shifts the ratio remarkably far to the isoindolenine side; however, the effect is not additive since the 1,3-dimethyl system has a smaller proportion of isoindole tautomer than the 1-methyl.<sup>16</sup> Aryl substituents in the 1,3-positions reestablish the isoindole tautomer (Table VI), presumably because conjugation between the aromatic systems is energetically more

TABLE VI  
 SUBSTITUENT EFFECTS ON TAUTOMERIC RATIO

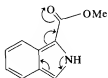
Substituents at		Solvent	Isoindole (%)	Reference
1	3			
H	H	$\text{CDCl}_3$ , $(\text{CD}_3)_2\text{CO}$ , $\text{CD}_3\text{CN}$ , $\text{C}_6\text{D}_5\text{CD}_3$	~100	6, 20
Me	H	$\text{C}_6\text{D}_6$	1	16
Me	Me	$\text{CDCl}_3$	20	16
OEt	H	$\text{CDCl}_3$	0	12, 25
Ph	H	$\text{CDCl}_3$	91	12
Ph	Ph	$\text{CDCl}_3$	~100	33
$\text{CO}_2\text{Me}$	H	$\text{CCl}_4$	~100	23
$\text{CO}_2\text{Me}$	$\text{CO}_2\text{Me}$	$\text{CDCl}_3$	~100	24

favorable than cross-conjugation of the benzophenone imine (i.e., aryl isoindolenine) type.

However, electron-donating substituents on the 1-phenyl group increase the proportion of isoindolenine (Table V). This effect, seen above with the 1-methyl compound, is a general one and reaches an extreme with powerful electron donors such as OEt and  $\text{NR}_2$ , where only the isoindolenine form is detected (e.g., **71**). For the NHR substituent a further structural problem arises between the two isomeric amidines (**72** and **73**). Although this problem does not appear to have been settled beyond dispute, in this review structure **73** will be used throughout.



Electron-withdrawing substituents at C-1 (C-3), conversely, favor the isoindole tautomer **74**. For the 1-methoxycarbonyl and 1,3-dimethoxycarbonyl derivatives, only the isoindole form is detected. The X-ray structure of 1-formyl-3-phenylisoindole<sup>95</sup> reveals the isoindole tautomer with a N—H bond length of 0.95 Å. The NMR spectrum in  $d_6$ -dimethyl sulfoxide shows a sharp signal at  $\delta 9.96$  (—CHO) and a broad signal at  $\delta 13.74$  (NH). The isoindolenine form is not detected.<sup>25</sup>



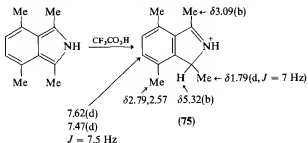
(74)

(arrows show stabilization of isoindole tautomer by electron-withdrawing group at C-1)

The effect of substituents in the six-membered ring is rather more complex. Thus, 4,5,6,7-tetrafluoroisoindole exists essentially as the isoindole tautomer in acetone<sup>45</sup>; other analogous halo derivatives behave similarly.<sup>34</sup> Tetra-alkyl substitution in this ring produced a significant amount of the isoindolenine tautomer (36% in benzene). The isoindole tautomer predominates for 4,7-dimethylisoindole, even in nonpolar solvents such as benzene. However, 5,6-dimethylisoindole appears to exist to a large extent as the isoindolenine structure in nonpolar solvents.<sup>36</sup> This may find rationalization in that calculations consistently show ground-state  $\pi$ -electron densities for the isoindole system to be higher at C-5 (C-6) than at C-4 (C-7) (Section IV.A; Table II).

### C. ACIDITY AND BASICITY

Isoindole would be expected to be a stronger base than pyrrole and to generate the isoindolenium ion (e.g., **75**) on protonation. This is confirmed by the spectra in trifluoroacetic acid of 1,3,4,7-tetramethylisoindole,<sup>78</sup> 4,5,6,7-

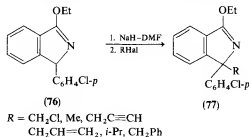


tetrabromoisoindole,<sup>35</sup> and 4,5,6,7-tetrachloroisoindole.<sup>34</sup> In dilute acid (0.5 M DCl/D<sub>2</sub>O), 2-methylisoindole polymerizes, but in concentrated sulfuric acid the isoindolenium cation is formed.<sup>103</sup> 2,5,6-Trimethyl-1,3-diphenylisoindole ( $\lambda_{\text{max}}$  226, 275, 282, 339, and 377 nm in ethanol) is protonated

<sup>103</sup> W. L. F. Armarego, B. A. Milloy, and S. C. Sharma, *J. C. S. Perkin I*, 2485 (1972).

to give the isoindolenine cation ( $\lambda_{\max}$  236, 303 nm) on adding 0.1 N HCl to the ethanolic solution, suggesting a  $pK_a \geq 1$ ; 5,6-dimethyl-1,2,3-triphenylisoindole is not appreciably protonated under these conditions.<sup>6,8</sup> Quantitative spectroscopic studies have provided  $pK_a$  values for two aryl-substituted isoindoles (2,5-dimethyl-1,3-diphenylisoindole,  $pK_a$  2.05; 4-methyl-1,2,3-triphenylisoindole  $pK_a$  -0.22).<sup>104</sup> 1-Methylisoindolenium hydrochloride has been observed in the electrochemical reduction of 1-methylphthalazine (Section III,D,1).<sup>13</sup>

There is little information on the acidity of isoindoles. Exchange of NH for ND occurs with deuterium oxide under neutral conditions<sup>34</sup> and in the presence of pyridine<sup>35</sup> and triethylamine.<sup>6</sup> 1-Phenylisoindole is not acidic enough to react with diazomethane, but 1-formyl-3-phenylisoindole is *N*-methylated by this reagent.<sup>25</sup> Treatment of 1,3,4,7-tetramethylisoindole with sodium hydride in dimethylformamide generates the anion, benzylation of which occurs at C-1.<sup>78</sup> Other examples of reactions of isoindole anions have been reported. Thus, acylation of the anions from 1-phenylisoindole<sup>83</sup> and 1-dialkylamino-2-arylisoindoles<sup>105</sup> occurs at C-3. On the other hand, the anion of 4,5,6,7-tetrafluoroisoindole reacts at nitrogen to afford the 2-benzyl derivative in 33% yield.<sup>45</sup> Generation of the anion from the isoindolenine **76** with sodium hydride-dimethylformamide, followed by alkylation, gives the 1,1-disubstituted-1*H*-isoindole **77**.<sup>106</sup>



## D. ELECTROPHILIC SUBSTITUTION

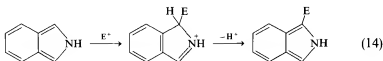
If aromatic electrophilic substitution is dependent on ground-state  $\pi$ -electron densities in the isoindole system (Section IV,A; Table II) then reaction would be expected to occur preferentially at C-1 (C-3), followed by

<sup>104</sup> M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, and R. D. Tack, *Tetrahedron* **32**, 1767 (1976).

<sup>105</sup> F. S. Babichev and A. K. Tyltin, *Ukr. Khim. Z.* **37**, 453 (1971) [*CA* **75**, 63540 (1971)].

<sup>106</sup> M. K. Eberle and W. J. Houlihan, *Tetrahedron Lett.*, 3167 (1970); M. K. Eberle, L. Brzechffa, and W. J. Houlihan, *J. Org. Chem.* **42**, 894 (1977).

reaction at C-5 (C-6). Reactions of the first type are known. There is no example at present of direct substitution into the six-membered ring. The reactions are all thought to proceed via the isoindolenium ion, which is equivalent to the Wheland intermediate for this series (Eq. 14). The electrophilic reagents need to be of the mildest, otherwise the isoindole system tends not to survive.



### 1. Deuteration

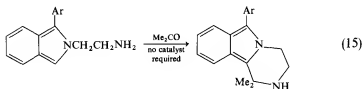
Deuteration at C-1 (C-3) has been observed to occur under mild conditions. Although it was not observed with isoindole itself, it was detected with 1-phenylisoindole ( $D_2O$ , room temperature).<sup>20</sup> The reaction in these cases might involve the isoindole-isoindolenine tautomerization. With 2-methylisoindole this cannot be the case, and here the reaction has been observed in  $D_2O$ -dioxane at  $50^\circ C$  and is regarded as an electrophilic substitution.<sup>107</sup> The reaction has been followed by NMR spectroscopy; the signals attributable to the 2-methyl group and the hydrogens of the six-membered ring are not diminished. The apparent first-order rate constant for the diminution of the C-1 (C-3) signal is  $2.4 \times 10^{-3} \text{ sec}^{-1}$ ; this value is about 10,000 times greater than the rate constant for the analogous exchange at position 3 of 1-methylindole under the same conditions ( $k = 2.5 \times 10^{-7} \text{ sec}^{-1}$ ). This gives a useful comparison of reactivity with that of a familiar heterocyclic system.

### 2. Alkylation

Simple alkylations have been observed with the isoindole anion (Section V.C). Substituted alkyl groups have been introduced using the Mannich reaction. Thus, treatment of 2-methyl-1-phenylisoindole with formaldehyde and morpholine gives the 3-morpholinomethyl derivative.<sup>108</sup> The cyclization shown in Eq. (15) is a related reaction.<sup>51</sup> Attempts to carry out a Mannich reaction when a strongly electron-withdrawing methoxycarbonyl group is present at C-1 of the isoindole have been unsuccessful.<sup>23</sup> With 1-phenylisoindole the Mannich reaction proceeds further to give dibenzopyrromethene derivatives (Section V.F,2).

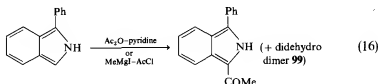
<sup>107</sup> W. Engewald, M. Mühlstädt, and C. Weiss, *Tetrahedron* **27**, 4171 (1971).

<sup>108</sup> W. Theilacker and H. Kalenda, *Justus Liebigs Ann. Chem.* **584**, 87 (1953).

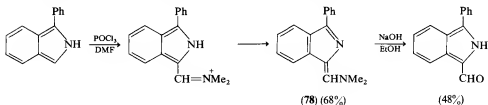


### 3. Acylation

Acetylation of 1-methoxycarbonylisoindole with acetic anhydride has been attempted without success.<sup>23</sup> However, 1-phenylisoindole can be acetylated (acetic anhydride-pyridine) to give the 3-acetyl derivative (Eq. 16).<sup>83</sup> An analogous reaction occurs with 2-alkyl-1-dialkylaminoisoindoles.<sup>105</sup>

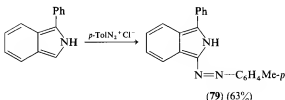


Vilsmeier formylation of 2-benzylisoindole gives the 1-formyl derivative (61%).<sup>25</sup> With 1-phenylisoindole reaction occurs at the unsubstituted  $\alpha$ -position; the intermediate iminium salt on neutralization gives the cross-conjugated enamine system **78**, which has been isolated and characterized. X-Ray analysis confirms the assigned structure.<sup>95</sup> On hydrolysis, the formyl derivative, which has also been the subject of X-ray crystal analysis (Figs. 4 and 5), is formed. As expected from the analogy with pyrrole chemistry, the aldehyde does not readily form typical carbonyl derivatives.



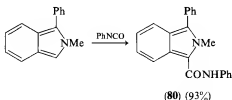
### 4. Diazonium Coupling

1-Phenylisoindole couples with *p*-tolyl diazonium chloride to give the azo derivative **79**.<sup>25</sup>



### 5. Carboxamidation

1,2-Disubstituted isoindoles react with phenyl isocyanate (or methyl isocyanate)<sup>83</sup> to give the products (80) of C-substitution.<sup>109,110</sup> Phenyl isothiocyanate gives the analogous thioamide.<sup>105</sup>



## E. CYCLOADDITION REACTIONS

Many isoindoles readily form Diels–Alder adducts by reaction across the electron-rich 1,3-positions with dienophiles. The importance of this reaction in practical terms has been considerable because it provides a way of trapping the isoindole system; and, unlike the isoindoles, the adducts are generally white crystalline solids which are easy to handle. The existence of the parent compound was first demonstrated in this way.<sup>14</sup> The reactions are considered below in terms of the various categories of dienophile.

### 1. Maleic Acid Derivatives

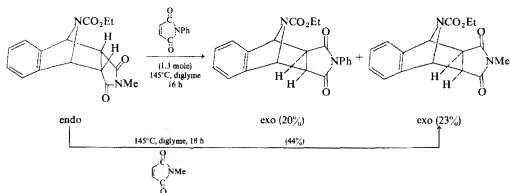
Adducts have been prepared with maleic anhydride (e.g., isoindole,<sup>14</sup> 2-benzylisoindole,<sup>30</sup> 1,3-diphenylisoindole<sup>33</sup>), *N*-phenylmaleimide [e.g., isoindole (Eq. 3),<sup>6</sup> 1-methylisoindole,<sup>16</sup> 2-benzylisoindole,<sup>30</sup> 4,5,6,7-tetrachloroisoindole<sup>34</sup>], and *N*-methylmaleimide (e.g., isoindole,<sup>17</sup> 2-*p*-tosylisoindole<sup>25</sup>). The stereochemistry of the adduct depends on the substitution

<sup>109</sup> W. Theilacker and W. Schmidt, *Justus Liebigs Ann. Chem.* **597**, 95 (1955).

<sup>110</sup> R. J. McCaully and S. C. Bell, U.S. Patent 3,736,318 (1973) [*CA* **80**, 82956 (1974)].

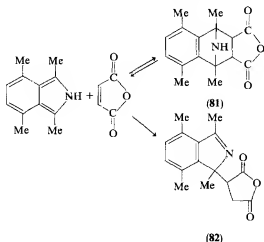


pattern and on the reaction conditions: where a bulky substituent is present (e.g., 2-benzyl-4,5,6,7-tetrafluoroisoindole) only the *endo* isomer may be seen.<sup>4,5</sup> It has been possible in some cases to isolate the *endo* isomer and convert it thermally to the *exo* isomer. Examples are given in Eq. (3) and in Scheme 13; the latter also furnishes an example of dienophile exchange.<sup>25</sup>



SCHEME 13

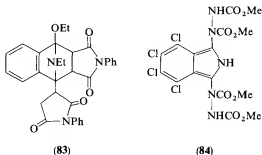
The reaction between 1,3,4,7-tetramethylisoindole and maleic anhydride in benzene initially deposits crystals of the Diels-Alder adduct **81**; on heating, this melts and then resolidifies to form the substitution product **82**. The same change occurs when **81** is kept in solution; in that case, the intermediate formation of the isoindole chromophore can be detected (Scheme 14).<sup>1,2</sup> The substitution reaction recalls pyrrole chemistry, where cycloaddition is much less common.



SCHEME 14

1-Phenylisindole initially follows the substitution pathway in its reaction with maleic anhydride.<sup>12</sup> 1,3-Diphenylisindole forms the cycloaddition product, but the reaction is readily reversed.<sup>33</sup>

As expected, electron-withdrawing substituents at carbon in the isindole structure slow down the cycloaddition to typical dienophiles. Thus, 4,5,6,7-tetrabromoisindole is reported not to form a maleic anhydride adduct,<sup>35</sup> and 2-methyl-4,5,6,7-tetrafluoroisindole has been observed to react more sluggishly with dienophiles than either isindole or 2-ethoxycarbonylisindole.<sup>17</sup> On the other hand, 2-alkyl-1-alkoxyisindoles give 1:2-adducts (e.g., **83**) in which *both* cycloaddition and substitution reactions have occurred.<sup>49</sup>



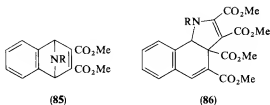
## 2. Azodicarboxylic Acid Esters

Although the result is not clearly stated in the paper, the tricyclic 4,5-disubstituted isindole **24** appears to give the cycloadduct with dimethyl azodicarboxylate.<sup>37</sup> 4,5,6,7-Tetrachloroisindole gives the disubstitution product **84** however.<sup>34</sup>

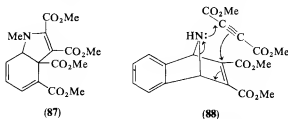
## 3. Dimethyl Acetylenedicarboxylate

Both 1:1 and 1:2 adducts are formed. The typical 1:1 adducts (**85**) have been observed with highly substituted systems, such as 2-benzyl-1,3,4,7-tetramethyl,<sup>111</sup> 1,2,3,4,7-pentamethyl,<sup>111</sup> and 2,4,7-trimethyl-1,3-diphenyl.<sup>111</sup> With 1,3,4,7-tetramethylisindole the 1:1 adduct is isolated with one molar equivalent of the dienophile; with a further molar equivalent of the dienophile the 1:2 adduct is formed.<sup>102</sup> The 1:2 adduct is assigned<sup>102</sup> the structural type **86**, which recalls that of the 1:2 adduct (**87**) formed when

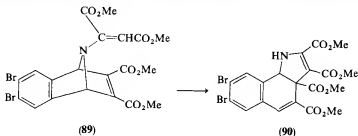
<sup>111</sup> L. J. Kricka and J. M. Vernon, *Chem. Commun.*, 942 (1971); *J. C. S. Perkin I*, 904 (1972).



1-methylpyrrole reacts with dimethyl acetylenedicarboxylate.<sup>112</sup> The formation of the 1:2 adduct is rationalized as shown at structure **88** and has been observed for the following isoindoles: 2-ethyl,<sup>111</sup> 2-butyl,<sup>111</sup> 5,6-dimethyl,<sup>36</sup> and 5,6-dibromo.<sup>35</sup> The rationalization (**88**) does not necessarily imply a concerted process: indeed, with certain *N*-unsubstituted isoindoles (e.g., 4,5,6,7-tetrachloro, 4,5,6,7-tetrabromo, 4,7-dibromo, 5,6-dibromo, 4,5,6,7-tetramethyl, and 4,7-dimethyl)<sup>34-36</sup> the products (e.g., **89**) of Michael addition



are isolated. In one case (that with 5,6-dibromo substitution), this Michael adduct isomerizes (**89** → **90**) to a structure of type **86**.<sup>35</sup> The 4,5,6,7-tetrachloro



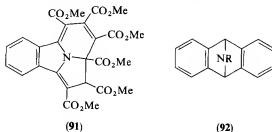
analog of **89** has been observed to give the 1:1 adduct under acidic conditions.<sup>34</sup>

The addition of the second molecule of the acetylenic ester thus appears to be very sensitive to steric factors,<sup>111</sup> especially insofar as the 2-substituent is concerned. Thus, attempts to react the 1,3,4,7-tetramethyl derivative of **85** (*R* = Me) with dimethyl acetylenedicarboxylate did not generate the analog of the 1:2 adduct (**86**), but gave the corresponding naphthalene-2,3-

<sup>112</sup> R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1148 (1962).

dicarboxylic acid ester; i.e., the reaction proceeded with the elimination of methylamine. This elimination was apparently induced by the dienophile since it did not occur when the 1:1 adduct was heated alone.<sup>111</sup>

It is appropriate to mention here that, although ethoxyisindolenine (Section V,J) does not take part in normal Diels–Alder additions, it does react with dimethyl acetylenedicarboxylate to give a 1:3 adduct, the structure of which (91) has been established by X-ray crystallography.<sup>57,113</sup>



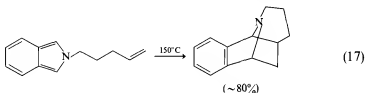
#### 4. Arynes

Benzyne and substituted benzyne react with isoindoles to give the 9,10-dihydroanthracene-9,10-imines (92).<sup>3,3</sup> A considerable number of substituted compounds of this type have been prepared.<sup>27</sup> Triptycene derivatives (i.e., the benzyne adducts of the anthracene system) have been encountered as unexpected products from the reaction of benzyne with 2-benzyl-1,3,4,7-tetramethylisindole.<sup>114</sup>

Aza analogs of 92 derived from 2,3-pyridynes and from 3,4-pyridynes have also been described.<sup>27</sup>

#### 5. Simple Olefins

Isoindoles undergo the Diels–Alder reaction readily, but there appears to be only one example of the reaction with simple olefins. This is a special, intramolecular, case where the frequency factor is high (Eq. 17).<sup>55</sup>



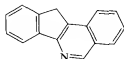
<sup>113</sup> H. J. Lindner and B. von Gross, *Z. Naturforsch., Teil B* **28**, 545 (1973).

<sup>114</sup> L. J. Kricka and J. M. Vernon, *J. C. S. Perkin I*, 766 (1973).

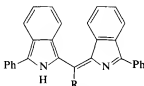
## F. SELF-CONDENSATION REACTIONS

1. *Pyrolysis*

Heating 2-methylisindole (230°C, 1 h) gives the tetracyclic compound (**93**) in 45% yield.<sup>115</sup>



(93)

(94) a, R = H; b, R = Ph  
c, R = Me; d, R = Et2. *Dibenzopyrromethene Formation*

Diphenyldibenzopyrromethenes (**94**), produced from isoindoles or their precursors on a number of occasions, possess a striking blue color and show a characteristic intensification and bathochromic shift of the visible absorption band on acidification (e.g., for **94a**, royal blue → turquoise blue;  $\lambda_{\max}$  588 → 629 nm).

In 1968, Australian workers<sup>116</sup> reported that the reaction of phenylmagnesium bromide with *trans*-*o*-cyano- $\beta$ -bromostyrene gave 1-phenylisoquinoline and an unstable blue substance to which they assigned structure **94a**. The same system, apparently previously unknown, was reported in the same year by two other groups. A Bulgarian group<sup>117</sup> showed that the reaction between 1-phenylisoindole and benzaldehyde gave **94b**; the same compound was obtained by the reaction of 2,3-diphenylindenone with ammonia under pressure. A Japanese group<sup>118</sup> prepared **94a**, **c**, and **d** from the reaction of ammonia with the appropriate *o*-acylbenzophenone under mildly acidic conditions. More recently, workers in Scotland have encountered **94a** as a by-product in the reaction of some diaryliminyl radicals.<sup>119</sup> These reactions are rationalized in Scheme 15, which also shows a rather more efficient synthesis of this system developed in London.

<sup>115</sup> W. Rettig and J. Wirz, *Helv. Chim. Acta* **61**, 444 (1978).

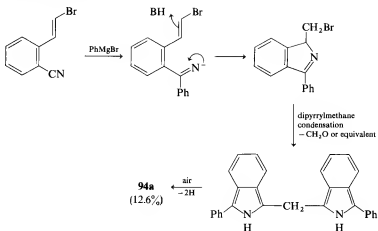
<sup>116</sup> G. M. Brown, R. G. Curtis, W. Davies, T. A. A. Dopheide, D. G. Hawthorne, J. R. Hlubucek, B. M. Holmes, J. F. Kefford, J. L. Osborne, A. V. Robertson, and E. C. Slater, *Aust. J. Chem.* **21**, 483 (1968).

<sup>117</sup> T. P. Ivanov and A. Draganov, *Monatsh. Chem.* **99**, 1990 (1968).

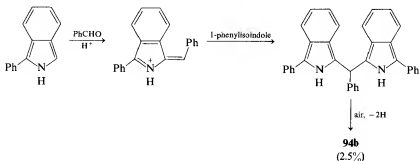
<sup>118</sup> E. Makeawa, Y. Suzuki, and S. Sugiyama, *Chem. Ber.* **101**, 847 (1968).

<sup>119</sup> A. R. Forrester, M. Gill, and R. M. Thomson, *J. C. S. Perkin I*, 621 (1979).

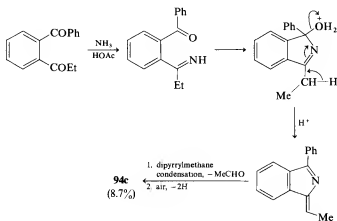
(i) Australian route<sup>116</sup>



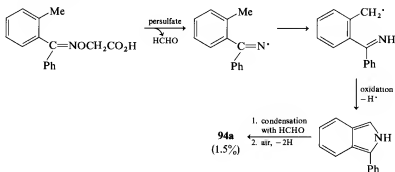
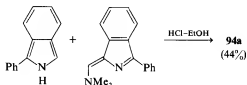
(ii) Bulgarian route<sup>117</sup>



(iii) Japanese route<sup>118</sup>

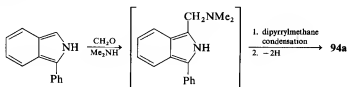


SCHEME 15

(iv) Caledonian route<sup>119</sup>(v) London route<sup>25</sup>

SCHEME 15 (continued)

Thus, the reaction of isoindoles with aldehydes and ketones when a reactive  $\alpha$ -carbon is introduced at C-1 (C-3) is likely to lead to a dibenzopyrromethene, especially so if one of the reactive 1 (3) positions is originally blocked by an aryl group. Thus, an attempt to carry out a Mannich reaction on 1-phenylisoindole (using  $\text{CH}_2\text{O}/\text{Me}_2\text{NH}$ , or  $\text{CH}_2=\text{NMe}_2^+\text{I}^-$ ) gives **94a** in 20% yield.<sup>25</sup>



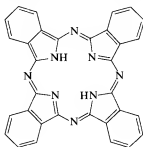
## 3. Macrocyclic Systems

Pyrrole is to porphyrin as isoindole is to tetrabenzoporphyrin. The tetrabenzoporphyrins and their tetra-*meso*-aza derivatives, the phthalocyanines, are extended aromatic systems of considerable thermodynamic stability. Because of this, they can sometimes be generated under rather

forcing conditions, under which they survive while less stable molecules are destroyed.

Phthalocyanines may conveniently be prepared by the self-condensation of 1,3-diiminoisoindoline (**40**, Scheme 6) or substituted derivatives. Heating **40** in a hydrogen-donor solvent (such as tetralin) causes ammonia to be eliminated, and the parent compound, phthalocyanine (**95**), is formed.<sup>120</sup> In the presence of metal salts, the corresponding metal phthalocyanines are generated, usually very efficiently. Some of these (e.g., the copper complex) are of commercial importance as blue and green pigments which are extremely light-stable.<sup>121</sup>

Other macrocyclic systems have been prepared by crossed condensations between 1,3-diiminoisoindoline and other heterocyclic bases.<sup>120,122</sup>



(95)

The ideal monomer for the synthesis of a symmetrically substituted tetrabenzoporphyrin by an analogous tetramerization would be expected to be the isoindole **96**. This substance has not been prepared, but the expectation of its usefulness is confirmed by the observation that 1,3,4,7-tetramethylisoindole is an excellent precursor, in spite of the fact that it appears to be structurally unsuitable in that it has one  $\alpha$ -methyl group too many. Thus, heating 1,3,4,7-tetramethylisoindole with nickel(II) acetate in 1,2,4-trichlorobenzene under reflux provides the nickel(II) octamethyltetrabenzoporphyrin (**97**) in 71% yield.<sup>123</sup> The transition metal ion has a template effect since without it only a small amount (5%) of the metal-free tetrabenzoporphyrin is formed. Various other metal complexes (Mg, Mn, Fe, Co, Cu) have been made this way.<sup>123,124</sup> An alternative route involves fusing the

<sup>120</sup> J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 3536 (1955).

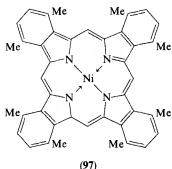
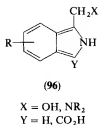
<sup>121</sup> F. H. Moser and A. L. Thomas, "Phthalocyanine Compounds," ACS Monogr. Ser., No. 157, van Nostrand-Reinhold, Princeton, New Jersey, 1963.

<sup>122</sup> E. g., J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 5008 (1952); P. F. Clark, J. A. Elvidge, and R. P. Linstead, *ibid.*, 3593 (1953).

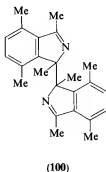
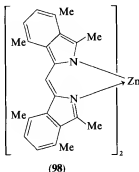
<sup>123</sup> C. O. Bender, R. Bonnett, and R. G. Smith, *J. C. S. Perkin I*, 771 (1972).

<sup>124</sup> J. R. Sams and T. B. Tsin, *Chem. Phys. Lett.* **25**, 599 (1974).





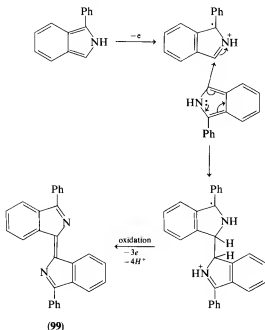
isoidole with a metal powder at a temperature of  $\sim 350^\circ\text{C}$ . This route works well for zinc and magnesium.<sup>102</sup> A mechanistic rationalization involving radical intermediates has been proposed for this remarkable reaction; in accord with this, methane and ethane are among the gaseous by-products.<sup>123</sup> With zinc(II) as the template ion, a tetrahedral zinc(II) dibenzopyrromethene complex (**98**, cf. **94**) has been obtained: this gives the zinc(II) octamethyltetrabenzoporphyrin complex on further heating.<sup>123</sup>



#### 4. Oxidative Dimerization

Under certain conditions (e.g., refluxing in benzene in the presence of air<sup>83</sup>; treatment with sodium nitrite-acetic acid<sup>25</sup>) 1-phenylisoidole gives a yellow substance which is formulated as the tetrahydro dimer **99**. This substance is thought to arise via the radical-cation as shown in Scheme 16. Alternative pathways can be envisaged. The tetrahydro dimer (**99**) has also been obtained by treating 3-phenylphthalimidine with thionyl chloride in dimethylformamide<sup>125</sup>; presumably, this reaction proceeds via the cyclic imidoyl chloride.

<sup>125</sup> W. L. F. Amarego and S. C. Sharma, *J. Chem. Soc. C*, 1600 (1970).



SCHEME 16

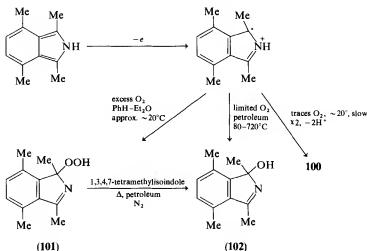
An analogous dimer (**100**), but at the didehydro oxidation level because further dehydrogenation is blocked, has been encountered with 1,3,4,7-tetramethylisoindole; it forms slowly on keeping the isoindole in an inert solvent in the dark.<sup>123</sup>

### G. OXIDATION

Isoindoles are readily oxidized; as with pyrroles, the products are often colored, poorly characterized, polymeric materials. Cyclic voltammetry of some of the more stable (arylated) isoindole systems has given peak potentials of about 0.7 V (vs. SCE) for one-electron oxidation. The radical-cations which are thus produced are remarkably long-lived (> 20 sec).<sup>126</sup>

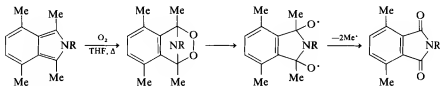
Autoxidation of 1,3,4,7-tetramethylisoindole with excess oxygen gives the hydroperoxide **101**. When oxygen supply is limited, the hydroxy derivative **102** is obtained. In an inert atmosphere the latter compound is formed by reaction of **101** with the isoindole.<sup>102</sup> In the presence of only traces of oxygen, the postulated radical-cation intermediate dimerizes to give **100** (Section V,F,4).<sup>123</sup>

<sup>126</sup> A. Zweig, G. Metzler, A. Maurer, and B. G. Roberts, *J. Am. Chem. Soc.* **89**, 4091 (1967).



SCHEME 17

A similar reaction sequence is observed with 4,7-dimethyl-1,3-diphenylisoindole.<sup>127</sup> Autoxidation of the anion from **76** also gives the corresponding 3-hydroxy derivative.<sup>106</sup> However, when the isoindole is 2-substituted, the reaction must take a different course since structures analogous to **101** and **102** are no longer possible. 2-Butylisoindole autoxidizes to give a mixture of 2-butyolphthalimide and 2-butyolphthalimidine. In solvents such as methyl isopropyl ketone, 2-butyloisoindoline autoxidizes to the same products, and 2-butyloisoindole is formed as an intermediate. The reaction is regarded as a radical chain process.<sup>128</sup> Various 2-alkyl- and 2-aryl-1,3,4,7-tetramethylisoindoles give the corresponding phthalimides.<sup>129</sup> It has been postulated that the reactions proceed through the *endo*-peroxide, with the loss of two methyl radicals (Eq. 18).<sup>129</sup>



R = Me, Et, CH<sub>2</sub>Ph, Ph

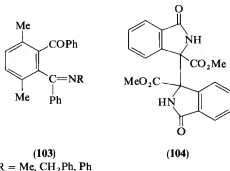
(18)

<sup>127</sup> M. Ahmed, L. J. Kricka, and J. M. Vernon, *J. C. S. Perkin I*, 71 (1975).

<sup>128</sup> J. K. Kochi and E. A. Singleton, *Tetrahedron* **24**, 4649 (1968).

<sup>129</sup> L. J. Kricka and J. M. Vernon, *J. Chem. Soc. C*, 2667 (1971).

An *endo*-peroxide has been isolated from the photochemical oxygenation of 1,2,3-triphenylisindole<sup>130</sup> and is also postulated as an intermediate in the autoxidation of various 2-substituted 4,7-dimethyl-1,3-diphenylisindoles, where the *o*-dibenzoylbenzene imines (**103**) are obtained.<sup>127</sup>



The 1-methoxycarbonylisindoles are much less easily autoxidized. However, in refluxing radical-initiating solvents such as methyl isobutyl ketone the corresponding phthalimidines are formed when a 2-substituent (Me, CH<sub>2</sub>Ph, Ph) is present. In the absence of a 2-substituent (i.e., with 1-methoxycarbonylisindole) the phthalimidine dimer **104** is obtained.<sup>23</sup>

## H. REDUCTION

A two-electron reduction of a number of arylisindoles has been observed to occur at a peak potential of approximately  $-2.4$  V (vs. SCE).<sup>126</sup> Isoindoles have been reduced by catalytic hydrogenation,<sup>4,131</sup> metal-acid systems (Zn-HOAc,<sup>12,33,45</sup> Sn-HCl<sup>132</sup>) and by cathodic reduction.<sup>13,126</sup> The isoindolines are generally formed cleanly. Thus, the reduction of 4,5,6,7-tetrafluoroisindole with zinc-copper couple in glacial acetic acid gives the corresponding isoindoline in 34% yield.<sup>45</sup> Treatment of 2,5-dimethylpyrrole with tin and hydrochloric acid, a reaction which presumably proceeds by way of 1,3,4,7-tetramethylisindole (Section III,E), gives a mixture of the *cis*- and *trans*-isoindolines, the former predominating.<sup>132,133</sup>

When a strongly electron-withdrawing group is present at C-1 (C-3), the reaction may take a different course. Thus, the catalytic reduction of 1-methoxycarbonyl- and 1,3-dimethoxycarbonylisindoles occurs in the six-membered ring to generate 4,5,6,7-tetrahydroisindoles; i.e., the pyrrole

<sup>130</sup> W. Theilacker and W. Schmidt, *Justus Liebigs Ann. Chem.* **605**, 43 (1957).

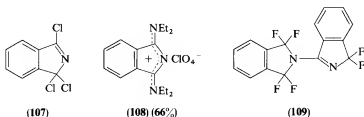
<sup>131</sup> G. Wittig and H. Streib, *Justus Liebigs Ann. Chem.* **584**, 1 (1953).

<sup>132</sup> R. Bonnett and J. D. White, *J. Chem. Soc.*, 1648 (1963).

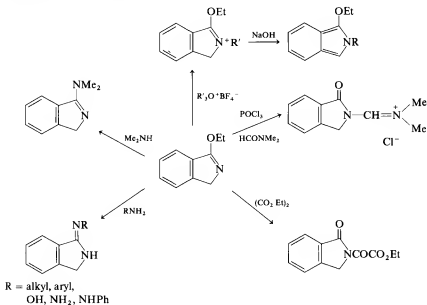
<sup>133</sup> R. Bonnett and C. O. Bender, *J. Chem. Soc.*, 2186 (1968).



trifluoride or hydrogen fluoride affords the fluorinated dimer **109**. The reaction also occurs with some substituted derivatives.<sup>136</sup>



Ethoxyisindolenine behaves as a cyclic imidate. As shown in Scheme 18, it reacts with certain nucleophilic reagents at C-1, while electrophilic reagents tend to attack N-2.<sup>25,57</sup>



SCHEME 18

## ACKNOWLEDGMENTS

We thank Dr. A. D. McNaught (Royal Society of Chemistry, London) for advice on nomenclature. We find it convenient to retain the term isindolenine for general discussion, since it makes a clearer differentiation between the names of the tautomers. However, we have used the alternative term, 1H-isindole, for systematic nomenclature. We thank the Science Research Council, the Medical Research Council, and Glaxo Group Research Ltd. for support.

<sup>136</sup> L. M. Yagupolskii, V. B. Milevskaya, and R. V. Belinskaya, *Zh. Org. Khim.* **9**, 643 (1973) [*CA* **78**, 147727 (1973)].

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